IB04/04362

Europäisches Patentamt | European Patent Office | Office européen des brevets

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

03293309.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 03293309.5
Demande no:

Anmeldetag:
Date of filing: 23.12.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

NEURO3D
130, rue de la Mer Rouge
Bât. "la Fabrique" B.P. 42002
68058 Mulhouse Cedex 2
FRANCE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Phosphodiesterase inhibitors, preparation and therapeutic use thereof

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D243/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL
PT RO SE SI SK TR LI

Phosphodiesterase Inhibitors, Preparation and Therapeutic Use Thereof

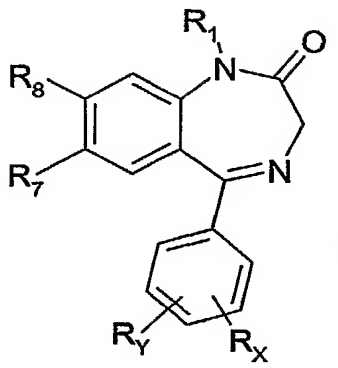
The invention relates to compounds and their uses, particularly in the pharmaceutical industry. The invention discloses compounds having PDE2 inhibitory activities, as well as therapeutic methods by administering said compounds, in particular for treating various diseases of the central or peripheral nervous system. It further deals with pharmaceutical compositions comprising said compounds and methods for preparing said compounds.

The compounds of the present invention present a very interesting pharmacological profile, since they are inhibitors of cyclic nucleotide phosphodiesterases and in particular cGS-PDE (cGMP-Stimulated PDEs, type 2-phosphodiesterase, or PDE2).

The intracellular second messenger cAMP or cGMP is broken down and deactivated by phosphodiesterase (PDE), which is classified into at least types I to XI. PDE is widely distributed in the tissue and organs of the body. Among these, type II phosphodiesterase breaks down both cAMP and cGMP and can be activated by cGMP. This type II phosphodiesterase is found in numerous tissues (adipocytes, brain, heart, lungs, kidneys, blood vessels, etc.). PDE2 inhibitors are able to increase or maintain intracellular cAMP and cGMP rates and thereby find therapeutic interests in various pathologies.

The present invention provides compounds having a high inhibiting activity on PDE2, and preferably a selectivity profile with respect to other PDE isoforms, including a low action on PDE3. This selectivity profile may extend to other types of enzymes, such as adenosine deaminase. Moreover, compounds of the invention present an interesting effect on the central nervous system (anticonvulsants, anxiolytics, sedative, antidepressants) or the peripheral nervous system (against rheumatism, autoinflammatory diseases, against dysfunction of liver due to ageing). They also avantageously present no perturbating effect on memory.

The present invention discloses therefore compounds having the following general formula (I) :



(I)

wherein :

. R_1 represents an hydrogen atom, (C_1-C_6) alkyl, aryl, (C_1-C_6)alkylaryl, aryl(C_1-C_6)alkyl group, (C_3-C_6) alkenyl, or (C_3-C_6) alkenylaryl,

. R_7 represents a, substituted or not substituted, aryl or heteroaryl group,

when R_7 is a substituted aryl, it is preferably mono or bis substituted by the following groups : a (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, (C_3-C_6)alkenyloxy, acyl, halogen, trifluoromethyl, difluoromethyl, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkylaryl, aryl, or -$CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen atom, an (C_1-C_6)alkyl group, (C_3-C_6)alkenyl group, an alkylaryl, an alkenylaryl, and an aryl group,

. R_8 represents a hydrogen atom or a OR_{10} group, wherein R_{10} is a hydrogen atom, an (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6) alkenyl, an (C_3-C_6)alkenylaryl, aryl, or heterocyclic group, aromatic or not, having 1 to 3 heteroatoms chosen between O, N, S,

when R_{10} is an aryl, it is preferably mono or bis substituted by the following groups : an hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, (C_3-C_6)alkenyloxy, halogen, trifluoromethyl, difluoromethyl, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkylaryl, aryl, and -$CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen

atom, an (C_1-C_6)alkyl group, (C_3-C_6)alkenyl group, an alkylaryl, an alkenylaryl, and an aryl group,

. R_X represents an hydrogen atom, an halogen atom, a methyl, a methoxy, an acetyl, a trifluoromethyl, CN, COH or $CONH_2$ group,

. R_Y represents an hydrogen, halogen atom, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, aryl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, alkenyl, (C_3-C_8)alkenyloxy, alkynyl, alkynyloxy, acyl, halogen, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NHCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkyloxy, hydroxy, (C_1-C_6)alkylaryl, aryl, or -$CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen atom, an (C_1-C_6)alkyl group, an (C_2-C_6)alkenyl group, an alkynyl, an alkylaryl, an alkenylaryl, an alkynylaryl, and an aryl group,
with the proviso that when R_8 is an hydrogen atom, then R_X or R_Y is different from hydrogen,
with the further proviso that when R_X or R_Y is halogen, it is not on position 2 of the phenyl,
or a pharmaceutically acceptable salt thereof.

The present invention also relates to pharmaceutical compositions comprising at least one compound as defined above in a pharmaceutically acceptable vehicle or support, optionally in association with another active agent.

The pharmaceutical composition is more particularly intended to treat diseases associated with abnormal regulation of intracellular cAMP and/or cGMP rate.

The present invention also relates to the use of a compound as defined above, for the preparation of a pharmaceutical composition for the treatment of diseases associated with abnormal regulation of intracellular cAMP and/or cGMP rate.

The present invention also includes methods of treating diseases associated with dysregulation of intracellular cAMP and/or cGMP rate, comprising the administration to a subject in need thereof of an effective amount of a compound as defined above.

Within the context of the present application, the alkyl groups may be linear or branched saturated groups containing from 1 to 10 carbon atoms. Examples of alkyl groups having from 1 to 10 carbon atoms inclusive are methyl, ethyl, propyl, isopropyl, t-butyl, n-butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, 2-ethylhexyl, 2-methylbutyl, 2-methylpentyl, 1-methylhexyl, 3-methylheptyl and the other isomeric forms thereof. Preferably, the alkyl groups have from 1 to 6 carbon atoms.

The term alkenyl denotes linear or branched groups containing from 2 to 6 carbon atoms and presenting at least one C=C double bond. Examples of alkenyl groups include in particular the allyl group.

The term alkynyl denotes linear or branched groups containing from 2 to 8 carbon atoms and presenting at least one C≡C triple bond. Examples of alkynyl groups include in particular the propynyl, butynyl, pentynyl, hexynyl group.

The term aryl includes any aromatic group comprising from 6 to 18 carbon atoms, preferably from 6 to 14 carbon atoms. Most preferred aryl groups are mono- or bi-cyclic and comprises from 6 to 10 carbon atoms, such as phenyl, α-naphtyl, β-naphtyl.

Another most preferred aryl group is tricyclic and includes antracenyl, or fluorenyl group. When R_7 is an aryl group, it is preferably phenyl, 1-naphtyl, or 2-naphtyl groups.

The term heteroaryl includes any aromatic group comprising from 4 to 18 carbon atoms, preferably from 4 to 14 carbon atoms, and interrupted by one or several heteroatoms selected from N, O, S. Most preferred heteroaryl groups are thienyl, benzothienyl, benzofuryl, pyridyl, pyrimidinyl, pyridazinyl, isoquinolyl, quinolyl, thiazolyl, furyl, pyranyl, pyrrolyl, 2*H*-pyrrolyl, imidazolyl, benzymidazolyl, pyrazolyl, isothiazolyl, isoxazolyl and indolyl groups.

The term arylalkyl (or aryl(C_1-C_6)alkyl) group generally stands for an aryl group attached to the molecule by an alkyl group as defined above, such as benzyl or

phenethyl. The term (C_1-C_6)alkylaryl group generally stands for an alkyl group attached to the molecule by an aryl group as defined above.

The term «cycloalkyl» denotes a cyclic saturated hydrocarbonated system, having preferably from 3-6 carbon atoms, mono- or poly-cyclic. Typical examples of such groups are cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group.

The term «heterocycle» includes any hydrocarbonated cycle, aromatic or not, having one or more cyclic heteroatoms. In particular, an heterocycle presents from 4 to 18 carbon atoms and one or more cyclic heteroatoms, such as N, O, or S. They include heteroaryl groups, such as thienyl, benzothienyl, benzofuryl, pyridyl, pyrimidinyl, pyridazinyl, isoquinolyl, quinolyl, thiazolyl, furyl, pyranyl, pyrrolyl, 2*H*-pyrrolyl, imidazolyl, benzimidazolyl, pyrazolyl, isothiazolyl, isoxazolyl, and indolyl groups. They also include non-aromatic heterocycles, such as morpholine, piperidine, piperazine, tetrahydrofuryl and pyrrolidine groups.

Halogen is understood to refer to fluorine, chlorine, bromine or iodine.

Heteroatom is understood to refer to O, N et S.

The term "acyl" denotes a radical of general formula RCO, wherein R represents an alkyl, alkenyl, aryl, heteroaryl, cycloalkyl, or heterocycle groups as defined above. In particular, the acyl group is an acetyl group.

The groups identified above may be substituted with at least one substituent, identical or different, preferably selected in the group consisting of an halogen atom, alkyl, halogenoalkyl, cycloalkyl, alkenyl, alkynyl, aralkyl, aryl, heterocycle, heterocycloalkyl, OH, =O, NO_2, CN, CF_3, COR', COOR', (C_1-C_6)alkoxy, -NR'R'', -NHCOR' and -CONR'R'' groups, wherein R' and R'' represent, independently from each other, are selected from the group consisting of a hydrogen atom, an alkyl group having from 1 to 10 carbon atoms, an aryl, an aralkyl group, (C_3-C_6)alkenyl, an alkylaryl and an (C_3-C_6)alkenylaryl.

According to a preferred embodiment, the compounds according to the invention correspond to general formula (I) wherein R_8 is an hydrogen atom, a methoxy, ethoxy or phenoxy group.

According to another preferred embodiment, the compounds according to the invention correspond to general formula (I), wherein at least one of R_X and R_Y is different from hydrogen.

According to another aspect of the invention, the compounds according to the invention correspond to general formula (I) wherein R_Y is an hydrogen atom and R_X is different from hydrogen.

According to another aspect of the invention, the compounds according to the invention correspond to general formula (I) wherein one of R_X and R_Y, different from hydrogen, is on position 3 of the phenyl group represented in formula (I).

According to another aspect of the invention, the compounds according to the invention correspond to general formula (I) wherein R_X, different from hydrogen, is on position 3 of the phenyl group represented in formula (I).

According to another aspect of the invention, the compounds according to the invention correspond to general formula (I) wherein R_X represents $CONH_2$ or CN group.

According to another embodiment, the compounds according to the invention correspond to formula (I) wherein R_Y represents H, an halogen atom, CF_3, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, -$NHCOR_{12}$, -$CONH_2$, a (C_1-C_6)alkyloxy group or a (C_1-C_6)alkyl group, preferably hydrogen.

According to a preferred embodiment, the compounds according to the invention correspond to general formula (I) wherein R_1 represents an alkyl group, preferably methyl, ethyl, or propyl, an alkenyl group, preferably propenyl, or arylalkyl group.

According to a preferred embodiment, when the compounds according to the invention correspond to general formula (I) wherein R_7 is a furan group, said group is preferably a furan-2-yl. When R_7 is a furan group, said group is preferably not substituted.

According to another preferred embodiment, the compounds according to the invention correspond to general formula (I) wherein R_7 is an unsubstituted aryl group, preferably unsubstituted phenyl group.

According to another aspect, the compounds according to the invention correspond to general formula (I) wherein R_7 is a substituted aryl or heteroaryl group, preferably a substituted phenyl group. In particular, said substituted aryl or heteroaryl group is substituted with one or two, identical or different, substituents. Said substituents are preferably selected in the group consisting of halogen, amino, aminoacyl (or

$NCOR_{12}$ as defined above), $(C_1\text{-}C_6)$alkyl and $(C_1\text{-}C_6)$alkyloxy. The alkoxy group is preferably a methoxy or ethoxy group. In particular, the substituted phenyl group is selected in the group consisting of 4-methoxy-phenyl, 4-fluoro-phenyl, 2-methoxy-phenyl, 2-chloro-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 3-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2,6-dimethoxy-phenyl, 4-benzamide, 4-cyanophenyl, 2,4-dimethoxy-phenyl, 4-carboxamide-phenyl, 4-acetyl-phenyl, 2-isopropoxy-phenyl, and 3,4-dimethoxy-phenyl groups.

When the compounds according to the invention are in the forms of salts, they are preferably pharmaceutically acceptable salts. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, perchloric, boric, nitric acids, and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, and in Handbook of Pharmaceutical Salts: Properties, Selection, and Use edited by P. Heinrich Stahl and Camille G. Wermuth 2002, which are incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamineoline and the like.

Specific examples of compounds of formula (I) which fall within the scope of the present invention include the following compounds:

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(3-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(4-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

8-Ethoxy-1-ethyl-5,7-diphenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-(1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(3-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzaldehyde

3-(8-Methoxy-7-(4-benzamide)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

5-(3-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(2-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(4-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(8-Methoxy-1-methyl-2-oxo-7-(4-cyanophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile.

5-(3-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-Acetyl-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(4-Acetyl-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(4-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(2-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(7-Furan-2-yl-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(3,5-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3,4-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(4-Fluoro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Acetyl-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-7-phenyl-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-5-(4-methyl-3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-7-phenyl-5-(4-trifluoromethoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Bromo-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[7-(2-Isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(3,4-Dimethoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

7-(2,6-Dimethoxy-phenyl)-5-(4-methoxy-phenyl)-1-methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

8-Methoxy-5-(4-methoxy-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

7-(2,6-Dimethoxy-phenyl)-1-methyl-5-(4-methyl-3-nitro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-5-(3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Amino-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin
-2-one
3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-
benzonitrile
3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzonitrile
3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzonitrile
3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzonitrile
3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzonitrile
3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-
benzamide
3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzamide
3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]-benzamide
3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]- benzamide
3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-
benzo[e][1,4]diazepin-5-yl]- benzamide
5-(3-Hex-1-ynyl-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]
diazepin-2-one
{3-[3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-
yl)-phenyl]-prop-2-ynyl}-carbamic acid tert-butyl ester.

Particularly preferred compounds are 3-[7-(2,6-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[7-(2,5-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[8-methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[8-methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[7-(2-chloro-phenyl)-8-methoxy-1-methyl-2-

oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide and 3-(8-methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide.

Particularly most preferred compounds are 3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide and 3-[8-methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide.

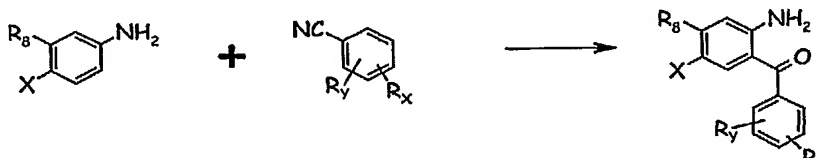
The compounds according to the present invention may be prepared by various methods known to those skilled in the art. Different chemical routes have been carried out and are described below.

Intermediates of general formula **II**, in which R_8 is OCH_3 or a OPh can be prepared using a method analogous to that reported in J. Med. Chem. 1989, Vol. 32, N°8, 1936-1942.

When R_8 is an ethoxy or an other alkoxy group, the synthesis of **II** could be performed starting from alkylation of 3-nitrophenol followed by reduction of the nitro group and then using the reference above.

When X is an aryl group and R8 is a methoxy group, the synthesis of II could be performed by a Suzuki coupling between 2-bromo-5-nitroanisole and a suitable boronic acid followed by reduction of the nitro group and then using the reference cited above.

Scheme 1



II **III** **IV**

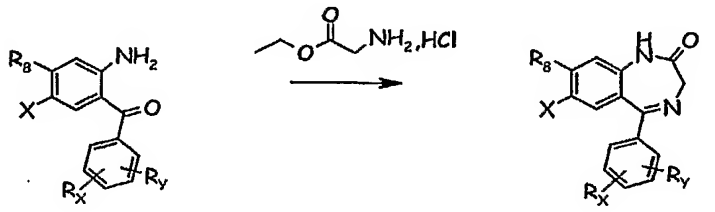
Intermediates of general formula IV	X	R_8	R_X	Ry
1	Br	OCH_3	3-CN	H
2	Br	H	3-CN	H
3	I	H	3-CN	H
4	Br	OC_2H_5	H	H
13	Br	OPh	3-CN	H

16	Ph	OCH_3	3-Br	H
19	Ph	OCH_3	H	4-OCH_3

For R_8 = H, the compounds **II** are commercially available.

The key intermediates of general formula **IV** can be obtained by a Sugasawa reaction (Scheme 1) from intermediates of general formula **II**, in which R_8 is as described above, and X is halogen and intermediates of general formula **III**, in which R_X and R_Y are as described above, in a suitable halogenated or aromatic solvent such as dichloromethane, trichloroethylenelorobenzene, toluene, xylene and most preferably 1,2-dichloroethane with a mixture of Lewis acid such as $GaCl_3/BCl_3$, $InCl_3/BCl_3$, $FeCl_3/BCl_3$, $SbCl_5/BCl_3$, $AgOTf/BCl_3$ and most preferably $AlCl_3/BCl_3$, followed by hydrolysis in HCl.

Scheme 2



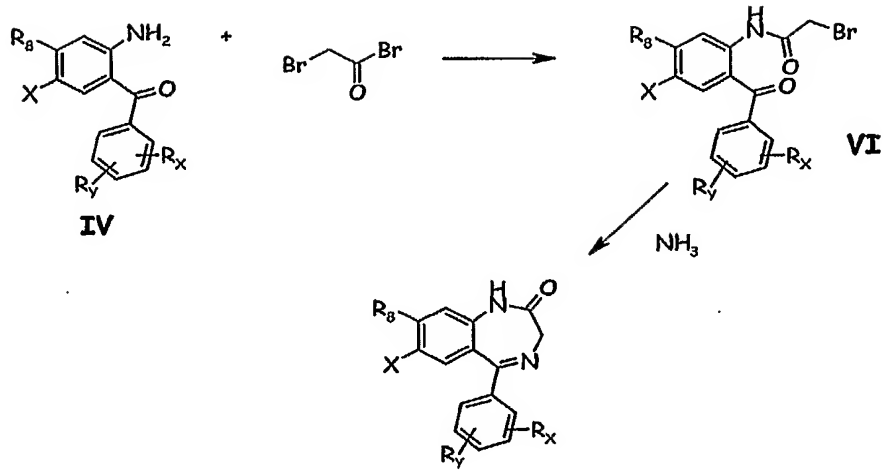
IV **V or I (Example 78)**

Intermediates of general formula V	X	R_8	R_X	R_Y
5	Br	OCH_3	3-CN	H
6	Br	OC_2H_5	H	H
7	I	H	3-CN	H
14	Br	OPh	3-CN	H
Example of general formula I	X	R_8	R_X	R_Y
76	Ph	OCH_3	H	4-OCH_3

Intermediates of general formula **V** in which R_8, X and R_X and R_Y have the same meaning as above can be prepared by heating intermediates of general formula **IV** and ethyl glycinate hydrochloride in Pyridine (Scheme 2).

For Example 76, the meaning of X is the same as R_7.

Scheme 3

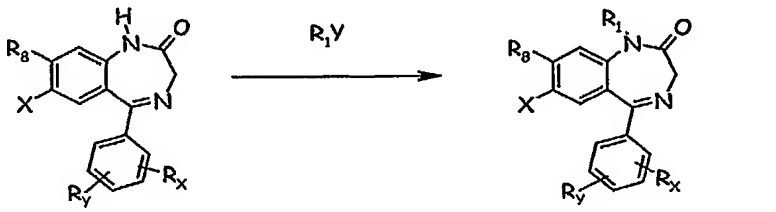


V or I (Example 80)

Intermediates of general formula V	X	R_8	R_X	R_Y
8	Br	H	3-CN	H
Example of general formula I	X	R_8	R_X	R_Y
80	Ph	OCH_3	3-Br	H

An alternative synthesis of intermediates of general formula **V** in which R_8 and R'_3 have the same meaning as above can also be performed in two steps by treating intermediates of general formula **IV** with bromoacetyl bromide (Scheme 3), followed by ammonia. For Example 80, the meaning of X is the same as R_7.

Scheme 4



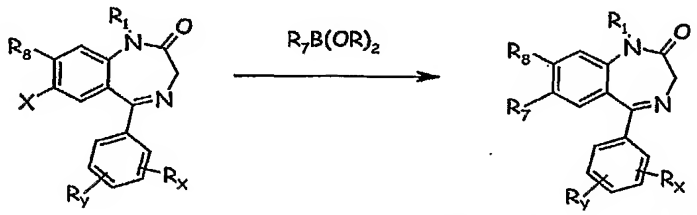
V **VII or I (Example 62)**

Intermediates of general formula **VII**	X	R_8	R_X	R_Y	R_1
9	Br	OCH_3	3-CN	H	CH_3
10	Br	H	3-CN	H	CH_3
11	I	H	3-CN	H	CH_3
12	Br	OC_2H_5	H	H	C_2H_5
15	Br	OC_2H_5	H	H	C_2H_5
Example of general formula **I**	X	R_8	RX	RY	R_1
62	Ph	OCH_3	3-Br	H	CH_3

Compounds of general formula **VII**, in which R_8 and R_X are as described above can be obtained by using an alkylating agent of general formula R_1Y, in which R_1 is as described above, and Y can be a suitable leaving group such as a chlorine, bromine, iodine, mesylate and tosylate, in phase transfer conditions. The reaction can be carried out in a suitable solvent such as halogenated hydrocarbons, toluene at room temperature or at boiling point.

For Example 62, the meaning of X is the same as R_7.

Scheme 5



VII **I (Examples 1-8,10-18, 48, 52,53 and 69-71)**

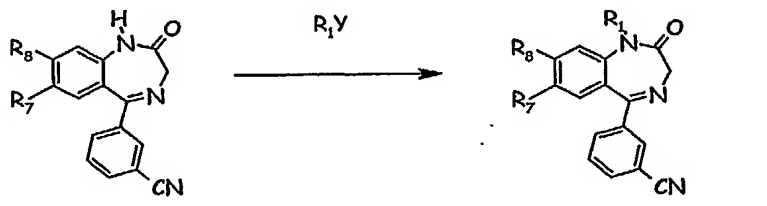
Examples of general formula **I**	R_8	R_X	R_1	R_7	R_Y
1	OCH_3	3-CN	CH_3	Ph	H
2	OCH_3	3-CN	CH_3	4-FPh	H
3	OCH_3	3-CN	CH_3	2-MeOPh	H
4	OCH_3	3-CN	CH_3	4-MeOPh	H
5	OCH_3	3-CN	CH_3	2-ClPh	H
6	OCH_3	3-CN	CH_3	3-ClPh	H
7	OCH_3	3-CN	CH_3	4-ClPh	H

8	OCH_3	3-CN	CH_3	Furo-2-yl	H
10	OCH_3	3-CN	H	2-MeOPh	H
11	H	3-CN	CH_3	Ph	H
12	H	3-CN	CH_3	2-MeOPh	H
13	H	3-CN	CH_3	3-MeOPh	H
14	H	3-CN	CH_3	4-MeOPh	H
15	H	3-CN	CH_3	2,5-DiMeOPh	H
16	H	3-CN	CH_3	2,6-DiMeOPh	H
17	H	3-CN	CH_3	2,4-DiMeOPh	H
18	OC_2H_5	H	C_2H_5	Ph	H
43	OCH_3	3-CN	CH_3	4-CNPh	H
48	OCH_3	3-CN	CH_3	4-CH_3COPh	H
52	H	3-CN	CH_3	Furo-2-yl	H
53	H	3-CN	CH_3	3,4-DiMeOPh	H
63	OCH_3	3-CN	CH_3	2-$(CH_3)_2$CHOPh	H
69	OPh	3-CN	CH_3	Ph	H
70	O-(2-MeO)Ph	3-CN	CH_3	Ph	H
71	O-(2-Cl)Ph	3-CN	CH_3	Ph	H
81	H	3-CN	CH_3	(2-Cl,6-MeO)Ph	H
82	H	3-CN	CH_3	(5-Cl,2-MeO)Ph	H

Compounds of general formula **I** can be prepared by using a Palladium catalysed cross-coupling between compounds **VII**, in which R_8 and R_X are as described above, (scheme 5) and boronic acids or esters $R_7B(OR)_2$, in which R_7 has the meaning as described above and R represents H, alkoxy or both R form with the boron atom and oxygen atoms a 6-membered ring.

X is an halogen atom, preferably bromine or iodine.

Scheme 6

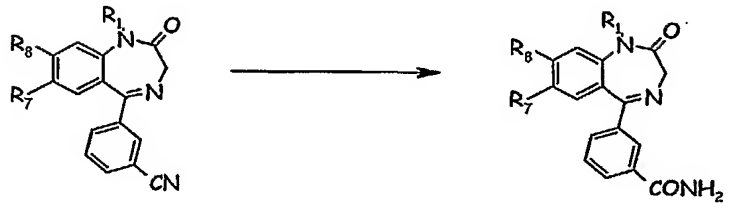


I **I (Examples 35-39)**

When R_1 is an hydrogen, compounds of general formula (I) can be converted in another series of general formula (I) by using an alkylating agent of general formula R_1Y, in which R_1 is as described above, and Y can be a suitable leaving group such as a chlorine, bromine, iodine, mesylate and tosylate, in phase transfer conditions. The reaction can be carried out in a suitable solvent such as halogenated hydrocarbons, toluene at room temperature or at boiling point.

Examples of general formula I	R_8	R_1	R_7
35	OCH_3	hexyl	2-MeOPh
37	OCH_3	propyl	2-MeOPh
38	OCH_3	$(CH_2)_2Ph$	2-MeOPh
39	OCH_3	CH_2Ph	2-MeOPh

Scheme 7



I **I (Examples 19-34 and 36)**

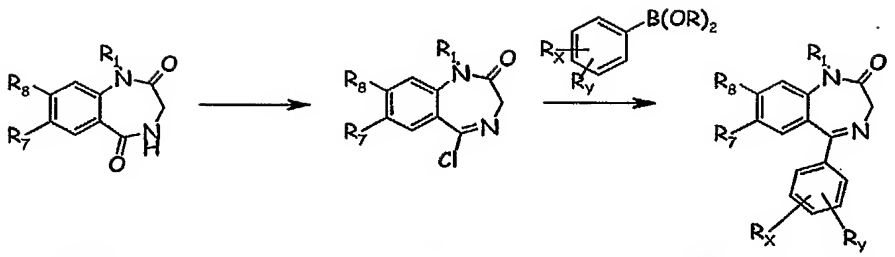
Examples of general formula I	R_8	R_1	R_7
19	OCH_3	CH_3	Ph
20	OCH_3	CH_3	4-FPh
21	OCH_3	CH_3	2-MeOPh
22	OCH_3	CH_3	4-MeOPh
23	OCH_3	CH_3	2-ClPh
24	OCH_3	CH_3	3-ClPh
25	OCH_3	CH_3	4-ClPh
26	OCH_3	CH_3	Furo-2-yl
27	H	CH_3	Ph
28	H	CH_3	2-MeOPh
29	H	CH_3	3-MeOPh
30	H	CH_3	4-MeOPh

31	H	CH_3	2,5-DiMeOPh
32	H	CH_3	2,6-DiMeOPh
33	H	CH_3	2,4-DiMeOPh
34	OCH_3	CH_3	4-$CONH_2$Ph
44	OCH_3	$PhCH_2$	2-MeOPh
45	OCH_3	$CH3(CH_2)_2$	2-MeOPh
46	OCH_3	$Ph(CH_2)_2$	2-MeOPh
47	OCH_3	$CH3(CH_2)_5$	2-MeOPh
49	OCH_3	CH_3	4-$COCH_3$Ph
54	H	CH_3	3,4-DiMeOPh
72	PhO	CH_3	Ph
73	PhO	CH_3	2-ClPh
74	PhO	CH_3	2-MeOPh
78	OCH_3	CH_3	2-($CH_3(CH_2)_2$)OPh
83	H	CH_3	(2-Cl,6-MeO)Ph
84	H	CH_3	(5-Cl,2-MeO)Ph

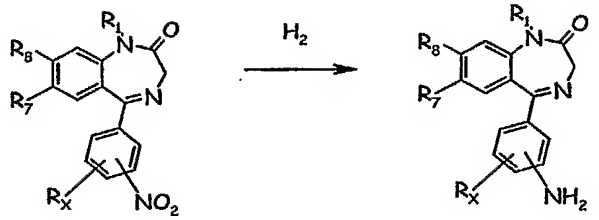
Compounds of general formula **I** (examples 19-34 and 36), in which R_8, R_1 have the same meaning as above and R_X is an amide can be prepared by oxidation with hydrogen peroxide and sodium hydroxide (0.5 M) in ethanol at room temperature or 60°C from compounds of general formula **I** in which R'$_3$ is a cyano.

Alternatively compounds I (examples 19-34 and 36) in which R_8, R_1 have the same meaning as above and R_X is an amide could also be prepared using sulphuric acid at a temperature between 20°C and 100°C from compounds of general formula I in which R_X is a cyano.

Scheme 8



VIII **IX** **I (Examples 9 and 40-42)**



I **I (Examples 68)**

Examples of general formula I	R_8	R_7	R_X	R_Y	R_1
9	H	Ph	3-CHO	H	CH_3
40	H	Ph	3-Cl	H	CH_3
41	H	Ph	2-Cl	H	CH_3
42	H	Ph	4-Cl	H	CH_3
50	H	Ph	H	4-OCH_3	CH_3
51	H	Ph	H	2-OCH_3	CH_3
55	H	Ph	3-Cl	5-Cl	CH_3
56	H	Ph	3-Cl	4-Cl	CH_3
57	H	Ph	4-F	H	CH_3
58	H	Ph	H	3-$COCH_3$	CH_3
59	H	Ph	3-CF_3	H	CH_3
60	H	Ph	3-CH_3	NO_2	CH_3
61	H	Ph	H	3-OCF_3	CH_3
64	H	Ph	3-OCH_3	4-OCH_3	CH_3
65	H	Ph	H	NO_2	CH_3
68	H	Ph	H	NH_2	CH_3
75	H	(2,6-DiMeO)Ph	H	4-OCH_3	CH_3
77	H	(2,6-DiMeO)Ph	3-CH_3	NO_2	CH_3

Compounds of general formula **VIII**, in which R_8 and R_1 are as described above can be obtained using the procedure describe in J.Med.Chem. 42, 5241-5253 (1999).

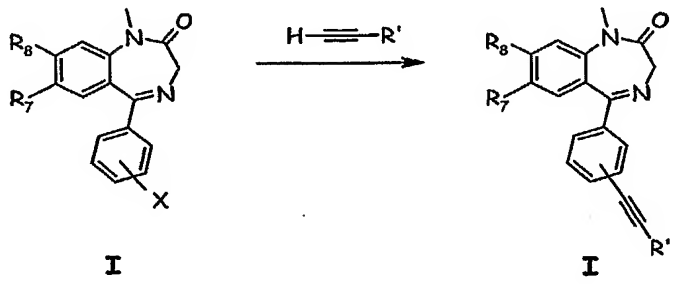
Compounds of general formula **IX**, in which R_8 and R_1 are as described above can be obtained by reacting compound of general formula **VIII** with $POCl_3$ and dimethylaniline in an halogenate solvent such as dichloromethane, 1,2-dichloroethane chlorobenzene and most preferably chloroform in a sealed tube at a temperature between 80°C to 130°C.

Compounds of general formula **I** can be prepared by using a Palladium catalysed cross-coupling between compounds **IX**, in which R_8 and R_1 are as described above, (scheme 7) and boronics acids or esters $R_XR_YPhB(OR)_2$, in which R_X and R_Y have the meaning as described above and R represents H, alkoxy or both R form with the boron atom and oxygen atoms a 6-membered ring,

X is an halogen atom, preferably chlorine.

Nitro compounds of general formula **I** was reduced by Palladium catalysed hydrogenation to provide amino group (Example 68).

Scheme 9



I **I**

Examples of general formula I	R_8	R_7	R'
66	OCH_3	Ph	butyl
67	OCH_3	Ph	CH_2NHBoc

Compounds of general formula (I) can be converted in another series of compounds of general formula (I) by using a Sonogashira Palladium catalysed cross-coupling (scheme 9), in which R_8 and R_7 are as described above, with substituted alkynes in which R' is an alkyl, arylalkyl, hydroxyalkyl, alkoxyalkyl, aminoalkyl, amidoalkyl and carbamoylalkyl. X is an halogen atom, preferably bromine or iodine.

It should be understood that other methods of producing these compounds may be designed by the skilled person, based on common general knowledge and following guidance contained in this application.

As indicated above, a further object of this invention relates to a pharmaceutical composition comprising at least one compound of formula (I), as defined above, and a pharmaceutically acceptable vehicle or support.

The compounds may be formulated in various forms, including solid and liquid forms, such as tablets, gel, syrup, powder, aerosol, etc.

The compositions of this invention may contain physiologically acceptable diluents, fillers, lubricants, excipients, solvents, binders, stabilizers, and the like. Diluents that may be used in the compositions include but are not limited to dicalcium phosphate, calcium sulphate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch, powdered sugar and for prolonged release tablet-hydroxy propyl methyl cellulose (HPMC). The binders that may be used in the compositions include but are not limited to starch, gelatin and fillers such as sucrose, glucose, dextrose and lactose.
Natural and synthetic gums that may be used in the compositions include but are not limited to sodium alginate, ghatti gum, carboxymethyl cellulose, methyl cellulose, polyvinyl pyrrolidone and veegum. Excipients that may be used in the compositions include but are not limited to microcrystalline cellulose, calcium sulfate, dicalcium phosphate, starch, magnesium stearate, lactose, and sucrose. Stabilizers that may be used include but are not limited to polysaccharides such as acacia, agar, alginic acid, guar gum and tragacanth, amphotsics such as gelatin and synthetic and semi-synthetic polymers such as carbomer resins, cellulose ethers and carboxymethyl chitin.
Solvents that may be used include but are not limited to Ringers solution, water, distilled water, dimethyl sulfoxide to 50% in water, propylene glycol (neat or in water), phosphate buffered saline, balanced salt solution, glycol and other conventional fluids.

The dosages and dosage regimen in which the compounds of formula (I) are administered will vary according to the dosage form, mode of administration, the

condition being treated and particulars of the patient being treated. Accordingly, optimal therapeutic concentrations will be best determined at the time and place through experimentation.

The compounds according to the invention can also be used enterally. Orally, the compounds according to the invention are suitable administered at the rate of 100 µg to 100 mg per day per kg of body weight. The required dose can be administered in one or more portions. For oral administration, suitable forms are, for example, tablets, gel, aerosols, pills, dragees, syrups, suspensions, emulsions, solutions, powders and granules; a preferred method of administration consists in using a suitable form containing from 1 mg to about 500 mg of active substance.

The compounds according to the invention can also be administered parenterally in the form of solutions or suspensions for intravenous or intramuscular perfusions or injections. In that case, the compounds according to the invention are generally administered at the rate of about 10 µg to 10 mg per day per kg of body weight; a preferred method of administration consists of using solutions or suspensions containing approximately from 0.01 mg to 1 mg of active substance per ml.

For the compounds of this invention, the dose to be administered, whether a single dose, multiple dose, or a daily dose, will of course vary with the particular compound employed because of the varying potency of the compound, the chosen route of administration, the size of the recipient, the type of disease and the nature of the patient's condition. The dosage to be administered is not subject to definite bounds, but it will usually be an effective amount, or the equivalent on a molar basis of the pharmacologically active free form produced from a dosage formulation upon the metabolic release of the active drug to achieve its desired pharmacological and physiological effects. A doctor skilled in the art for treating the disease will be able to ascertain, without undue experimentation, appropriate protocols for the effective administration of the compounds of this present invention, such as by referring to the earlier published studies on compounds found to have effect on the disease to be treated.

According to another aspect, the present invention relates to a method for the treatment of a disease associated with abnormal regulation of intracellular cAMP and/or cGMP rate, comprising administering to a patient in need of such treatment an effective amount of at least one compound of general formula (I) as described above.

Preferred compounds for use according to the invention include any sub-group or compound as defined above.

Compounds according to the invention may act advantageously on PDE2. Compounds of the invention are preferably selective inhibitors of PDE2, i.e. they present an inhibiting effect on other phosphodiesterases, including for instance PDE3 and PDE4 to a lesser extent. Some compounds present also a specific inhibiting profile for PDE2, including with respect to adenosine deaminase, and present to this respect advantageous therapeutic properties.

Compounds of formula (I) are more particularly useful to treat diseases of the central nervous system, especially connected with an abnormal regulation of neurotransmitter effect or a release deficiency of one of the neurotransmitters (e.g. dopamine, noradrenaline, acetylcholine, ...). In particular, they can be used to treat a disease selected in the group consisting of depression, schizophrenia, autism, anxiety, bipolar disorder, attention deficit hyperactivity disorder (ADHD), sleeping disorders, obsessive compulsive disorders (OCD), fibromyalgia, Tourette's syndrome, drug or alcohol dependence, epilepsia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, obesity, and Lewy body dementia.

According to another aspect, compounds of formula (I) are more particularly useful to treat diseases of the peripheral nervous system or peripheral organs, including reduced natriuria pathologies, acute renal or liver failure, liverdysfunction, and pathologies due to or involving prolactin release dysfunction, such as restless leg syndrome, rheumatic, allergic or autoinflammatory disorders, such as rheumatoid arthritis, rhinitis, and asthma.

The present invention deals also with the use of compounds of the invention, or compositions comprising the same, as anxiolytics, anti-convulsants, sedative or to treat memory deficiency or cognitive disorders.

The present invention deals also with the use of compounds of the invention, or compositions comprising the same, to treat neuro-degenerative diseases.

The present invention concerns furthermore the use of such compounds for the treatment to treat obesity.

According to the invention, the term treatment denotes curative, symptomatic, and preventive treatment. Such compounds, compositions comprising the same, or treatment can be implemented alone or in combination with other active ingredients, compositions or treatments. Moreover, it can correspond to treatment of chronic or acute disorders.

Figures

Figure 1 : Swim test results expressed as mean duration of phases of immobility (s) with different concentrations of a compound according to the invention

The invention is illustrated by the following examples. However, they are representative only and should not be construed as being limiting in any respect.

In the Preparations and Examples, unless otherwise stated:

Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded on Bruker Avance DRX 200 and 300 MHz. Chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard, and are assigned as singlets (s), doublets(d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m).

The chromatographic analysis conditions were: column Waters XTerra MS C18 (4.6 x 30mm, 5µm); flow rate 1.0mL/min; mobil phase: aqueous solution of 0,05% TFA (B) and acetonitrile.

The melting point has been performed using a capillary melting point apparatus ref : 7SMP3-0 Bibby.

EXAMPLES

EXAMPLE A

Preparation of intermediates of general formula IV (Scheme 1)

Intermediate 1

3-(2-Amino-5-bromo-4-methoxy-benzoyl)-benzonitrile

A solution of 4-bromo-3-methoxy-phenylamine (3 g, 14.85 mmol), in dichloroethane (15 mL) was added dropwise to an ice-cold stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 16.3 mL, 16.3 mmoles) under argon atmosphere.

Then were added isophtalonitrile (3.8 g, 29.70 mmoles) and anhydrous $AlCl_3$ (2.17 g, 16.30 mmoles) and the mixture was stirred at room temperature for 30 min. The mixture was then slowly heated to 60°C and CH_2Cl_2 removed by distillation. Then the solution was refluxed at 78°C for 16 hours. The reaction was allowed to cool to room temperature, treated with aqueous 2N HCl (28 mL) and heated at 78°C for 3 hours. Extraction of the mixture with CH_2Cl_2 (2 X 50 mL) and removal of the solvent afforded the intermediate 1 as a crude mixture. The crude material was chromatographed through silica gel (eluant : CH_2Cl_2 100% then AcOEt/Hexane: 1/1). The title compound (3 g) was obtained as a white solid in 61% yield.

TLC: (AcOEt/hexane:1/1): Rf : 0.7

^1H NMR ($CDCl_3$, 300 MHz): δ 7.87-7.77 (m, 3H), 7.63-7.58 (m, 1H), 7.46 (s, 1H), 6.48 (s-broad, 2H), 6.20 (s, 1H), 3.93 (s, 3H).

Intermediate 2

3-(2-Amino-5-bromo-benzoyl)-benzonitrile

Prepared from 4-bromo-phenylamine, using the same method described for Intermediate 1. The title compound (2.7g) was obtained as a yellow solid in 40% yield.

TLC: (AcOEt/CH_2Cl_2/hexane:1/2/4): Rf : 0,5.

^1H NMR ($CDCl_3$, 200 MHz): δ 7.96-7.81 (m, 3H), 7.70-7.62 (m, 1H 7.41-7.38 (m, 1H), 7.46 (m, 1H), 6.70-6.66 (m, 1H), 6.22 (s-broad, 2H).

Intermediate 3

3-(2-Amino-5-iodo-benzoyl)-benzonitrile

Prepared from 4-iodo-phenylamine, using the same method described for Intermediate 1. The title compound (3.4g) was obtained as a yellow solid in 37% yield.

TLC: (AcOEt/CH_2Cl_2:1/4): Rf : 0,6.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96-7.81 (m, 3H), 7.64-7.52 (m, 1H), 6.59-6.56 (m, 1H), 6.22 (s-broad, 2H).

Intermediate 4

(2-Amino-5-bromo-4-ethoxy-phenyl)-phenyl-methanone

A solution of 4-bromo-3-ethoxy-phenylamine (1.4g, 6.48 mmol), in dichloroethane (8 mL) was added dropwise to an ice-cold stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 6.87 mL, 9.72 mmoles) under argon atmosphere.

Then benzonitrile (1 mL, 9.72 mmoles) and anhydrous $AlCl_3$ (0.950 g, 7.12 mmoles) were added and the mixture was stirred at room temperature for 30 min. The mixture was then slowly heated to 60°C and CH_2Cl_2 removed by distillation. Then the solution was refluxed at 78°C for 16 hours. The reaction was allowed to cool to room temperature, treated with aqueous 2N HCl (14 mL) and heated at 78°C for 3 hours. Extraction of the mixture with CH_2Cl_2 (2 X 25 mL) and removal of the solvent afforded the Intermediate 4 as a crude mixture. The crude material was chromatographied : eluant : AcOEt/Hexane: 2/1 then 1/1. The title compound (1.1 g) was obtained as a pale yellow solid in 53% yield.

TLC: (AcOEt/hexane:1/1): Rf : 0.7

^{1}H RMN ($CDCl_3$, 200MHz) : δ 7.9-7.4 (m, 6H), 6.41 (s-broad, 2H), 6.20 (s, 1 H), 4.20-4.10 (m, 2H), 1.06-1.49 (m, 3H).

Intermediate 13

3-(2-Amino-5-bromo-4-phenoxy-benzoyl)-benzonitrile

Prepared from 4-bromo-3-phenoxy-phenylamine, using the same method described for Intermediate 1. The title compound (3.1 g) was obtained as a yellow solid, (yield = 39%).

Rf (Hex/CH_2Cl_2 : 1/3) : 0,4

^1H NMR ($CDCl_3$, 200 MHz): δ 7.80-7.77 (m, 3H arom), 7.62-7.37 (m, 4H arom), 7.27-7.23 (m, 1H arom), 7.10-7.06 (m, 2H arom), 6.22 (large s, 2H, NH_2), 5.99 (s, 1H arom).

Intermediate 16

3-(2-Amino-5-phenyl-benzoyl)-(3-bromo)phenyl-methanone

A solution of 2-phenyl-5-aminoanisole (1.77 g, 8.89 mmol), in dichloroethane (35 mL) was added dropwise to an ice-cold stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 9.42 mL, 9.42 mmoles) under argon atmosphere.

Then 3-bromobenzonitrile (2.427 g, 13.334 mmoles) and anhydrous $AlCl_3$ (1.3 g, 9.777 mmoles) were added and the mixture was stirred at room temperature for 30 min. The mixture was then slowly heated to 60°C and CH_2Cl_2 removed by distillation. Then the solution was refluxed at 78°C for 16 hours. The reaction was allowed to cool to room temperature, treated with aqueous 2N HCl (30 mL) and heated at 78°C for 3 hours. Extraction of the mixture with CH_2Cl_2 (2 X 35 mL) and removal of the solvent afforded the Intermediate 16 as a crude mixture. The crude material was purified by flash chromatography (eluant : AcOEt/Hexane: 2/1). The title compound (1.81 g) was obtained as a pale yellow solid in 53% yield.

TLC: (AcOEt/hexane:1/2): Rf : 0.4

^1H RMN ($CDCl_3$, 200MHz) :δ 7.81-7.74 (m, 1H), 7.62-7.48 (2H), 7.37-7.27 (m, 7H), 3.85 (s, 1H)

Intermediate 19

3-(2-Amino-5-phenyl-benzoyl)-(4-methoxy)phenyl-methanone

A solution of 2-phenyl-5-aminoanisole (1.0 g, 5.02 mmoles), in 1,2-dichloroethane (8 mL) was added dropwise to an ice-cold stirred solution of BCl_3 (1.0 M in CH_2Cl_2, 5.31 mL, 5.31 mmoles) under argon atmosphere.

Then p-methoxybenzonitrile (1.0 g, 7.53 mmoles) and anhydrous $AlCl_3$ (0.74 g, 5.52 mmoles) were added and the mixture was stirred at room temperature for 30 min. The mixture was then slowly heated at 60°C and CH_2Cl_2 removed by distillation. Then the solution was refluxed at 78°C for 16 hours. The reaction was allowed to cool to room temperature, treated with aqueous 2N HCl (20 mL) and heated at 78°C for 3 hours. Extraction of the mixture with CH_2Cl_2 (2 X 20 mL) and removal of the solvent afforded the Intermediate 19 as a crude mixture. The crude material was purified by flash chromatography (eluant : AcOEt/Hexane: 2/1). The title compound (1.14 g) was obtained as a pale yellow solid in 68%yield.

^1H RMN ($CDCl_3$, 300MHz) : δ 7.76-7.65 (m, 2H), 7.49 (s, 1H), 7.43-7.25 (m, 5H), 6.97-6.93 (m, 2H), 6.40-6.20 (m, 2H), 3.87 (s, 6H).

Preparation of intermediates of general formula V (Scheme 2)

Intermediate 5

3-(7-Bromo-8-methoxy-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

A mixture of glycine ethyl ester hydrochloride (2.26 g, 16.20 mmol) and Intermediate 1 (2.68 g, 8.10 mmol) in dry pyridine (30 mL) was refluxed with stirring for 16 hours. One equivalent of glycine ethyl ester hydrochloride was added after 4h, 8h and 24h. Removal of the pyridine under vacuum distillation afforded a crude which was partitioned between ethyl acetate (100 mL) / H_2O (100 mL). The aqueous phase was extracted one time with 100 mL of ethyl acetate; the combined organic phases were dried over Na_2SO_4, filtered and evaporated until dryness. The crude material was chromatographied : eluant : AcOEt/Hexane: 1/1. The title compound (2 g) was obtained as a white solid (yield = 54%).

TLC: (AcOEt/Hexane : 1/1) : Rf : 0.1

^1H NMR ($CDCl_3$, 200 MHz): δ 9.41 (s-broad, 1H), 7.91 (m, 1H), 7.79-7.75 (m, 2H), 7.58-7.50 (m, 1H), 7.41 (s, 1H), 6.67 (s, 1H), 4.36 (s-broad, 2H), 4.00 (s, 3H).

Intermediate 6

7-bromo-8-ethoxy-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from (2-amino-5-bromo-4-ethoxy-phenyl)-phenylmethanone Intermediate 4 using the same conditions used to prepare Intermediate 5. The title compound was obtained as a beige solid (yield = 24%).

TLC: (AcOEt/Hexane : 1/1) : Rf : 0,28

1H NMR ($CDCl_3$, 300 MHz): δ 10.00 (s-broad, 1H), 7.58-7.51 (m, 2H), 7.49-7.44 (m, 2H), 7.43-7.36 (m, 2H), 6.65 (s, 1H), 4.6-4.3 (m, 2H), 4.2-3.9 (m, 2H), 1.57-1.46 (m, 3H).

Intermediate 7

3-(7-Iodo-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(2-amino-5-iodo-benzoyl)-benzonitrile Intermediate 3 using the same conditions used to prepare Intermediate 5. The title compound (1.85g) was obtained as a beige solid, (yield = 55%).

TLC: (AcOEt/CH_2Cl_2 : 9/1) : Rf : 0,6

^{1}H NMR (DMSO-d_6, 200 MHz): δ 10.69 (s-broad, 1H), 8.01-7.88 (m, 3H), 7.78-7.67 (m, 2H), 7.53 (s, 1H), 7.11-7.06 (m, 1H), 4.20 (s-broad, 2H).

Intermediate 14

3-(7-Bromo-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(2-amino-5-bromo-4-phenoxy-benzoyl)-benzonitrile Intermediate 13 using the same conditions used to prepare Intermediate 5. The title compound (1.7g) was obtained as a beige solid, (yield = 60%).

Rf (AcOEt/CH_2Cl_2 : 1/2) : 0,4

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.53 (s, 1H, NH), 7.90 (s, 1H arom), 7.81-7.76 (m, 2H arom), 7.58-7.44 (m, 4H arom), 7.31-7.27 (m, 1H arom), 7.14-7.11 (m, 2H arom), 6.50 (s, 1H arom), 4.29 (s large, 2H, CH_2).

Example 76

5-(4-Methoxy-phenyl)-8-methoxy-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 3-(2-amino-5-phenyl-benzoyl)-(4-methoxy)phenyl-methanone Intermediate 19 using the same conditions used to prepare Intermediate 5. The title compound (0.36g) was obtained as a beige solid, (yield = 28%).

1H NMR (CDCl3, 300 MHz): δ 7.56-7.53 (m, =2H), 7.45-7.28 (s, 6H), 6.90-6.87 (s, 2H), 6.68 (s, 1H), 4.35 (broad s, 2H), 3.90(s, 3H), 3.84 (s, 3H).

Preparation of intermediates of general formula V (Scheme 3)

Intermediate 8

3-(7-Bromo-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

To a solution of 3-(2-Amino-5-bromo-benzoyl)-benzonitrile Intermediate 2 (10 mmoles) in methylene chloride (20 mL) at 0-5°C, were added bromoacetyl bromide (1.05 mL, 12 mmoles) and dropwise a solution of Na_2CO_3 10% aq. (11.70 mL). The solution was stirred at this temperature for 30 min. The two layers were separated; the organic layer was washed with water (20 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure to a crude which was stirred in NH_3 (7N)/MeOH (30mL) at O°C for 2-4 hours and then refluxed for 16 hours. The working solution was evaporated in vacuum, then triturated in water (100 mL) and filtered. The title compound (320mg) was obtained as a brown solid in 62% yield.

TLC: (AcOEt/CH_2Cl_2 : 1/2) : Rf :0,4

^1H NMR ($CDCl_3$, 200 MHz): δ 9.35 (s-broad, 1H), 7.91 (s, 1H), 7.89-7.75 (m, 3H), 7.51-7.50 (m, 1H), 7.37 (s, 1H), 7.14-7.09 (m, 1H), 4.36 (s-broad, 2H).

Example 80

5-(3-Bromo-phenyl)-8-methoxy-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 3-(2-Amino-5-phenyl-benzoyl)-(3-bromo)phenyl-methanone Intermediate 19 using the same conditions used to prepare Intermediate 16. The title compound (1.98g) was obtained as a pale yellow solid, (yield = 90%).

Rf (Hexane/EtAOc: 1/1)=0.2

RMN (CDCl3), (200Hz) :d 9.49 (s broad, 1H), 7.86 (s, 1H),, 7.66-7.21 (m, 9H), 6.89 (s, 1H), 4.35 (s, 2H), 3.93 (s, 3H).

Preparation of intermediates of general formula VII (Scheme 4)

Intermediate 9

3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

To a mixture of toluene (20 mL) and Aliquat 336 (20 µL) was introduced methyl iodide (337 µL, 5.41 mmoles) while the mixture was agitated, powdered 3-(7-bromo-8-methoxy-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 5 (1 g, 2.7 mmoles) and 50% aqueous sodium hydroxide (3.1 mL) were added to the reaction mixture. The two-phase system was stirred vigorously for 4 hours. The phases were separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic extracts were washed with cold water (10 mL); then the organic phase were dried over Na_2SO_4 and concentrated to dryness. The title compound (0.93g) was crystallised from MeOH/Diisopropylether to afford a white powder in 90% yield .

TLC: (AcOEt/Hexane : 1/1) : Rf : 0.2

^1H NMR ($CDCl_3$, 200 MHz): δ 7.91-7.86 (m, 2H), 7.79-7.75 (m, 1H), 7.59-7.51 (m, 1H), 7.40 (s, 1H), 6.81 (s, 1H), 4.89-4.84 and 3.83-3.78 (AB system, J = 11 Hz), 4.02 (s, 3H), 3.44 (s, 3H).

Intermediate 10

3-(7-Bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 8 using the same method described for Intermediate 9. The title compound (220mg) was obtained as a yellow solid (yield = 88%).

TLC: ($AcOEt/CH_2Cl_2$: 4/1) : Rf : 0,7

^1H NMR ($CDCl_3$, 300 MHz): δ 7.92-7.87 (m, 2H), 7.79-7.75 (m, 2H), 7.59-7.51 (m, 1H), 7.37-7.36 (m, 1H), 7.29-7.27 (m, 1H), 4.90-4.87 and 3.81-3.77 (AB system, J = 11 Hz), 3.41 (s, 3H).

Intermediate 11

3-(7-Iodo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile

Prepared from 3-(7-iodo-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 7 using the same method described for Intermediate 9. The title compound (1.55g) was obtained as a yellow solid (yield = 83%).

TLC: ($AcOEt/CH_2Cl_2$: 2/1) : Rf : 0,5

^1H NMR ($CDCl_3$, 200 MHz): δ 7.91-7.75 (m, 4H), 7.59-7.53 (m, 2H), 7.16-7.12 (m, 1H), 4.90-4.84 and 3.81-3.78 (AB system, J = 11 Hz), 3.39 (s, 3H).

Intermediate 12

7-bromo-8-ethoxy-1-ethyl-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 3-(7-bromo-8-ethoxy-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzene Intermediate 6 using the same method described for Intermediate 9. The title compound was obtained as a beige solid (yield = 80%).

TLC: (AcOEt/Hexane : 1/1) : Rf : 0,47

^1H NMR ($CDCl_3$, 200 MHz): δ 7.60-7.53 (m, 2H), 7.47-7.35 (m, 4H), 6.82 (s, 1H), 4.78-4.74 and 4.38-4.14 (AB system, J = 11 Hz, 4H), 3.82-3.62 (m, 2H), 1.60-1.50 (m, 3H), 1.13-1.09 (m, 3H).

Intermediate 15

3-(7-Bromo-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 14 using the same method described for Intermediate 9. The title compound (1.5g) was obtained as a yellow solid (yield = 97%).

Rf ($AcOEt/CH_2Cl_2$: 1/2) : 0,5

^1H NMR ($CDCl_3$, 200 MHz): δ 7.93 (s, 1H), 7.98-7.76 (m, 2H), 7.61-7.44 (m, 4H), 7.32-7.27 (m, 1H), 7.15-7.11 (m, 2H), 6.72 (s, 1H), 4.29 (s large, 2H), 4.88-4.83 and 3.84-3.78 (AB system, J = 11 Hz, 2H), 3.20 (s, 3H).

Example 62

5-(3-Bromo-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-(3-Bromo-phenyl)-8-methoxy-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one Intermediate 80 using the same method described for Intermediate 9. The title compound (1.38g) was obtained as a pale yellow solid, (yield 68%).

1H NMR (CDCl3, 300 MHz): δ 7.87 (s, 1H), 7.57-7.53 (m, 2H), 7.46-7.21 (m, 7H), 6.86 (s, 1H), 4.87-4.83 and 3.90-3.86 (AB system, J = 10.5 Hz,2H), 3.94(s, 3H), 3.49 (s, 3H).

Preparation of examples of general formula I (Schemes 5 and 8)

Example 1

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

To 5 mL of degazed DMF were added 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 9 (200 mg, 0.52 mmol), benzene boronic acid (160 mg, 1.32 mmoles), tripotassium phosphate (300 mg, 1.42 mmol), $Pd(PPh_3)_4$ (30 mg, 0.03 mmoles). The mixture was stirred for 16 hours at

120°C under nitrogene atmosphere. The working solution was diluted ten times with water and extracted three times with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated until dryness. The residue was chromatographied : eluant : CH_2Cl_2/ Et_2O: 1/1. The obtained compound was crystallised from ether/pentane to afford the title compound (118 mg): white solid, (yield = 60%).

TLC: (AcOEt) : Rf : 0,6

^1H NMR ($CDCl_3$, 300 MHz): δ 7.96-7.92 (m, 2H), 7.74-7.71 (m, 1H), 7.54-7.52 (m, 1H), 7.44-7.35 (m, 5H), 7.15 (s, 1H), 6.88 (s, 1H), 4.90-4.86 and 3.91-3.88 (AB system, J = 11 Hz), 3.99 (s, 3H), 3.50 (s, 3H).

Example 2

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used p-fluorophenyl boronic acid. The title compound (66mg) was obtained as a white solid, (yield = 43%).

TLC: (AcOEt) : Rf :0,6

^1H NMR ($CDCl_3$, 200 MHz): δ 7.95-7.92 (m, 2H), 7.75-7.71 (m, 1H), 7.57-7.49 (m, 1H), 7.43-7.36 (m, 2H), 7.13-7.04 (m, 3H), 6.88 (s, 1H), 4.91-4.85 and 3.91-3.86 (AB system, J = 11 Hz), 3.95 (s, 3H), 3.49 (s, 3H).

Example 3

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used o-methoxyphenyl boronic acid. The title compound (80mg) was obtained as a white solid, in 50% yield.

TLC: (AcOEt) : Rf : 0,6

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.04-7.96 (m, 2H), 7.74-7.70 (m, 1H), 7.55-7.45 (m, 1H), 7.38-7.30 (m, 1H), 7.22-7.19 (m, 1H), 7.14 (s, 1H), 7.03-6.95 (m, 2H), 6.88 (s, 1H), 4.89-4.84 and 3.95-3.90 (AB system, J = 10 Hz), 3.90 (s, 3H), 3.82 (s, 3H), 3.50 (s, 3H).

Example 4

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used p-methoxyphenyl boronic acid. The title compound (85mg) was obtained as a white solid, (yield = 53%).
TLC: (AcOEt) : Rf : 0,6
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.96-7.92 (m, 2H), 7.74-7.71 (m, 1H), 7.55-7.48 (m, 1H), 7.39-7.35 (m, 2H), 7.12 (s, 1H), 6.96-6.91 (m, 2H), 6.87 (s, 1H), 4.90-4.84 and 3.91-3.86 (AB system, J = 11 Hz), 3.94 (s, 3H), 3.83 (s, 3H), 3.49 (s, 3H).

Example 5

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used o-chlorophenyl boronic acid. The title compound (107mg) was obtained as a white solid, (yield = 66%).
TLC: (AcOEt) : Rf : 0,6
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.97 (m, 2H), 7.74-7.44 (m, 6H), 7.09 (s, 1H), 6.89 (s, 1H), 4.91-4.86 and 3.94-3.89 (AB system, J = 11 Hz), 3.91 (s, 3H), 3.51 (s, 3H).

Example 6

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used m-chlorophenyl boronic acid. The title compound (58mg) was obtained as a white solid, (yield = 36%).

TLC: (AcOEt) : Rf : 0,6

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.95-7.91 (m, 2H), 7.75-7.72 (m, 1H), 7.55-7.50 (m, 1H), 7.43 (m, 1H), 7.32 (m, 3H), 7.13 (s, 1H), 6.88 (s, 1H), 4.90-4.87 and 3.89-3.86 (AB system, J = 11 Hz), 3.95 (s, 3H), 3.49 (s, 3H).

Example 7

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used p-chlorophenyl boronic acid. The title compound (48mg) was obtained as a white solid, (yield = 30%).

TLC: (AcOEt) : Rf : 0,6

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94-7.92 (m, 2H), 7.75-7.72 (m, 1H), 7.55-7.50 (m, 1H), 7.37 (m, 4H), 7.12 (s, 1H), 6.68 (s, 1H), 4.90-4.86 and 3.90-3.86 (AB system, J = 11 Hz), 3.95 (s, 3H), 3.49 (s, 3H).

Example 8

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example

1 and instead of using benzene boronic acid, we used furan-2-boronic acid. The title compound (40mg) was obtained as a white solid, (yield = 41%).

TLC: (AcOEt) : Rf : 0,6

1H NMR ($CDCl_3$, 200 MHz): δ 7.89-7.96 (m, 2H), 7.72-7.76 (m, 1H), 7.49-7.59 (m, 1H 7.15-7.19 (d, J = 9 Hz, 1H), 6.84-6.86 (d, J = 2 Hz, 1H), 6.75-6.80 (dd, J = 2 Hz and 9 Hz, 1H), 3.79-3.84 and 4.80-4.86 (AB system, J = 10 Hz,), 3.93 (s, 3H,), 3.42 (s, 3H).

Example 9

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzaldehyde

To 5 mL of degazed DMF were added 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one (200 mg, 0.52 mmol), 3-formylbenzene boronic acid (160 mg, 1.32 mmoles), tripotassium phosphate (300 mg, 1.42 mmol), $Pd(PPh_3)_4$ (30 mg, 0.03 mmoles). The mixture was stirred for 16 hours at 120°C under nitrogene atmosphere. The working solution was diluted ten times with water and extracted three times with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated until dryness. The residue was chromatographied : eluant : CH_2Cl_2/ Et_2O: 1/1. The title compound was crystallised from ether/pentane to afford the title compound (118 mg): white solid, (yield = 25%).

TLC: (Hexane/AcOEt: 3/1) : Rf : 0,10

1H NMR (CDCl3, 200 MHz): δ 10.05 (s, 1H), 8.17 (s,1H), 8.02-7.35 (m, 11H), 4.92-4.87 and 3.9-3.87 (AB system, J = 10 Hz, 2H), 3.48 (s, 3H).

Example 10

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 5 using the same method described for Example 1 and instead of using benzene boronic acid, we used 2-methoxy-benzene boronic acid.

The title compound (474mg) was obtained as a pale yellow solid, (yield = 88%).

TLC: (AcOEt/Hexane: 1/1): Rf : 0.1)

Example 11

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1.**
The title compound (82mg) was obtained as a yellow solid, (yield = 69%).
TLC:(AcOEt/CH_2Cl_2 : 4/1) : Rf : 0,4
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.98-7.92 (m, 2H), 7.85-7.73 (m, 2H), 7.57-7.40 (m, 7H), 4.92-4.87 and 3.91-3.86 (AB system, J = 11 Hz_2), 3.47 (s, 3H).

Example 12

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 2-methoxyphenyl boronic acid. The title compound (85mg) was obtained as a yellow solid, (yield = 45%).
TLC: (AcOEt/CH_2Cl_2 : 3/7) : Rf :0,3
^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.97-7.73 (m, 4H), 7.53-7.36 (m, 4H), 7.01-6.90 (m, 3H), 4.92-4.87 and 3.91-3.85 (AB system, J = 10 Hz_2), 3.85 (s, 3H), 3.47 (s, 3H).

Example 13

3-[7-(3-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 3-methoxyphenyl boronic acid. The title compound (110mg) was obtained as a yellow solid, (yield = 58%).
TLC: (AcOEt/CH_2Cl_2 : 3/7) : Rf : 0,3

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.06-8.01 (m, 2H), 7.76-7.73 (m, 2H), 7.57-7.40 (m, 3H), 7.27-7.23 (m,2H), 7.05-6.96 (m,2H), 4.91-4.85and 3.93-3.87 (AB system, J = 10 Hz_2), 3.82 (s, $3H_3$), 3.46 (s, $3H_3$).

Example 14

3-[7-(4-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 4-methoxyphenyl boronic acid. The title compound (90mg) was obtained as a yellow solid, (yield = 47%).

TLC: ($AcOEt/CH_2Cl_2$: 3/7) : Rf :0,3

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.99-7.94 (m, 2H), 7.80-7.76 (m, 2H), 7.56-7.50 (m, 1H), 7.45-7.36 (m, 4H), 6.98-6.95 (m, 2H), 4.90-4.87 and 3.90-3.84 (AB system, J = 10 Hz_2), 3.84 (s, 3H), 3.46 (s, 3H).

Example 15

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 2,5-dimethoxyphenyl boronic acid. The title compound was obtained as a yellow solid, (yield = 65%).

TLC: ($AcOEt/CH_2Cl_2$: 3/7) : Rf :0,3

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.05-8.01 (m, 2H), 7.77-7.73 (m, 2H), 7.56-7.51 (m, 1H), 7.44-7.41 (m, 3H), 6.89-6.82 (m, 3H), 4.90-4.86 and 3.92-3.88 (AB system, J = 10 Hz_2), 3.79 (s, 3H), 3.77 (s, 3H), 3.46 (s, 3H).

Example 16

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 2,6-dimethoxyphenyl boronic acid. The title compound (148mg) was obtained as a yellow solid, (yield = 71%).

TLC: ($AcOEt/CH_2Cl_2$: 3/7) : Rf : 0,3

^1H NMR ($CDCl_3$, 300 MHz): δ 8.13-8.10 (m, 1H), 7.98 (s, 1H), 7.75-7.73 (m, 1H), 7.63-7.51 (m, 2H), 7.43-7.40 (m, 1H), 7.33-7.27 (m, 2H), 6.66-6.63 (m, 2H), 4.90-4.86 and 3.99-3.95 (AB system, J = 10 Hz_2), 3.79 (s, 6H), 3.48 (s, 3H).

Example 17

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 14** using the same method described for **Example 1** and instead of using benzene boronic acid, we used 2,4-dimethoxyphenyl boronic acid. The title compound (135mg) was obtained as a yellow solid, (yield = 49%).

TLC: ($AcOEt/CH_2Cl_2$: 3/7) : Rf : 0,3

^1H NMR ($CDCl_3$, 300 MHz): δ 8.06-8.01 (m, 2H), 7.75-7.70 (m, 2H), 7.56-7.53 (m, 1H), 7.41-7.39 (m, 2H), 7.19-7.16 (m, 1H), 6.56-6.54 (m, 2H), 4.89-4.85 and 3.84-3.80 (AB system, J = 10 Hz_2), 3.84 (s, 3H), 3.80 (s, 3H), 3.46 (s, 3H).

Example 18

8-Ethoxy-1-ethyl-5,7-diphenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 7-bromo-8-ethoxy-1-ethyl-5-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one **Intermediate 16** using the same method described for **Example 1**.The title compound was obtained as a beige solid, (yield = 10%).

TLC: (Hexane/AcOEt: 1/1) : Rf :0,29

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.75-7.60 (m, 2H), 7.5-7.3 (m, 8H), 7.2-7.1 (m, 1H), 6.92 (s, 1H), 4.83-4.79 and 3.89-3.86(AB system, J = 10 Hz, 2H), 4.41-4.31 (m, 1H), 4.24-4.15 (m, 2H), 3.82-3.75 (m, 1H,), 1.5-1.4 (m, 3H), 1.3-1.1 (m, 3H).

Example 40

5-(3-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using benzene boronic acid, we used 3-chlorophenyl boronic acid. The title compound was obtained as a pale yellow solid (yield = 37%).

TLC: (Hexane/AcOEt: 31) : Rf : 0,22

1H NMR (CDCl3, 200 MHz): δ 7.81-7.72 (m, 2H), 7.70-7.28 (s,10H), 4.88-4.83 and 3.88-3.83 (AB system, J = 10.5 Hz,2H), 3.45 (s, 3H).

Example 41

5-(2-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using benzene boronic acid, we used 2-chlorophenyl boronic acid. The title compound (115mg) was obtained as a beige solid (yield = 61%).

TLC: (Hexane/AcOEt: 3/1) : Rf : 0,11

1H NMR (CDCl3, 200 MHz): δ 8.00-7.28 (m, 12H), 4.95-4.90 and 3.98-3.93 (AB system, J = 10.5 Hz,2H), 3.53 (s, 3H).

Example 42

5-(4-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 4-chlorophenyl boronic acid. The title compound was obtained as a pale yellow solid (yield = 35%).

TLC: (Hexane/AcOEt: 3/1) : Rf : 0,14

1H NMR (CDCl3, 200 MHz): δ 7.81-7.26 (m, 12H), 4.87-4.82 and 3.87-3.82 (AB system, J = 10.5 Hz,2H), 3.45 (s, 3H).

Example 43

3-(8-Methoxy-1-methyl-2-oxo-7-(4-cyanophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used 4-cyanophenyl boronic acid. The title compound (25mg) was obtained as a beige solid (yield = 14%).

TLC: (CH_2Cl_2/Et_2O: 1/1) : Rf :0,3

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.96-7.92 (m, 2H), 7.71-7.67 (m, 3H), 7.56-7.52 (m, 3H), 7.14 (s, 1H), 6.90 (s, 1H), 4.92-4.87 and 3.90-3.85 (AB system, J = 10 Hz), 3.96 (s, 3H), 3.50 (s, 3H).

Example 48

3-[7-(4-Acetylphenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used 4-acetylphenyl boronic acid. The title compound (83mg) was obtained as a pale green solid, (yield = 51%).

TLC: (Hexane/AcOEt: 1/1) : Rf :0,1

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.48 (m, 8H), 7.17 (s, 1H), 6.90 (s, 1H), 4.92-4.87 and 3.92-3.86 (AB system, J = 11 Hz), 3.96 (s, 3H), 3.50 (s, 3H), 2.62 (s, 3H).

Example 50

5-(4-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 4-methoxyphenyl boronic acid. The title compound (70mg) was obtained as a white solid, (yield = 47%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,35

1H NMR (CDCl3, 200 MHz): δ 7.80-7.27 (m, 10H), 6.93-6.89 (2s, 2H), 4.82-4.77 and 3.85-3.81 (AB system, J = 10.5 Hz,2H), 3.85 (s, 3H), 3.44 (s, 1H).

Example 51

5-(2-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 2-methoxyphenyl boronic acid. The title compound (87mg) was obtained as a beige solid (yield = 58%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,30

1H NMR (CDCl3, 200 MHz): δ 7.68-7.67 (m, 1H), 7.56-7.52 (s, 1H), 7.46-7.32 (m, 8H), 7.08-7.01 (m, 1H), 6.88-6.84 (m, 1H), 4.86-4.81 and 3.91-3.86 (AB system, J = 10.5 Hz, 2H), 3.51 (s, 3H), 3.48 (s, 1H).

Example 52

3-[7-(Furan-2-yl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-iodo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 11** using the same conditions used to prepare **Example 1** but using 2-furanboronic acid instead of benzene boronic acid. The title compound (10mg) was obtained as a brown solid (yield = 8%).

Rf (AcOEt/CH_2Cl_2 : 3/7) : 0,4

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92-7.73 (m, 4H), 7.57-7.37 (m, 1H), 4.92-4.85 and 3.91-3.86 (AB system, J = 10 Hz, 2H), 3.47 (s, 3H).

Example 53

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-iodo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 11** using the same conditions used to prepare **Example 1** but

using 3,4-dimethoxyphenyl boronic acid instead of benzene boronic acid. The title compound (110mg) was obtained as a beige solid, (yield = 72%).

Rf ($AcOEt/CH_2Cl_2$: 3/7) : 0,3

^1H NMR ($CDCl_3$, 300 MHz): δ 7.99-798 (m, 2H), 7.77-7.73 (m, 2H), 7.56-7.53 (m, 1H), 7.44-7.35 (m, 2H), 7.03-6.92 (m, 3H), 4.91-4.87 and 3.91-3.90 (AB system, J = 10 Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.46 (s, 3H).

Example 55

5-(3,5-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3,5-dichlorophenyl boronic acid.The title compound (34mg) was obtained as a beige solid, (yield = 22%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,20

1H NMR (CDCl3, 200 MHz): δ 7.87-7.82 (m, 1H), 7.60-7.40 (m, 10H), 4.93-4.88 and 3.91-3.86 (AB system, J = 10.5 Hz,2H), 3.49 (s, 3H).

Example 56

5-(3,4-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3,4-dichlorophenyl boronic acid. The title compound (46mg) was obtained as a beige solid, (yield = 30%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,13

1H NMR (CDCl3, 200 MHz): δ 7.88-7.82 (m, 2H), 7.48-7.40 (m, 9H), 4.92-4.87 and 3.91-3.86 (AB system, J = 10.5 Hz,2H), 3.49 (s, 3H).

Example 57

5-(4-Fluoro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene

boronic acid, we used 4-fluorophenyl boronic acid. The title compound (19mg) was obtained as a beige solid, (yield = 14%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,26

1H NMR (CDCl3, 300 MHz): δ 7.82-7.78 (m, 1H), 7.72-7.65 (m, 2H), 7.55-7.34 (m, 7H), 7.13-7.06 (m, 2H), 4.85-4.82 and 3.87-3.83 (AB system, J = 10.5 Hz,2H), 3.46 (s, 3H).

Example 58

5-(3-Acetyl-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3-acetylphenyl boronic acid. The title compound (44mg) was obtained as a beige solid, (yield = 31%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,25

1H NMR (CDCl3, 300 MHz): δ 8.30 (s, 1H), 8.10-8.00 (m, 1H), 7.98-7.75 (m, 2H), 7.52-7.34 (m, 8H), 4.91-4.87 and 3.91-3.87 (AB system, J = 10.5 Hz,2H), 3.48 (s, 3H), 2.64 (s, 3H).

Example 59

1-Methyl-7-phenyl-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3-trifluoromethylphenyl boronic acid. The title compound (30mg) was obtained as a beige solid, (yield = 20%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,1

1H NMR (CDCl3, 300 MHz): δ 8.05 (s, 1H), 7.92-7.70 (m, 3H), 7.51-7.30 (m, 8H), 4.92-4.88 and 3.91-3.87 (AB system, J = 10.5 Hz,2H), 3.50 (s, 3H).

Example 60

1-Methyl-5-(4-methyl-3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used (4-methyl-3-nitro)phenyl boronic acid. The title compound (36mg) was obtained as a beige solid, (yield = 24%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,1

1H NMR (CDCl3, 300 MHz): δ 8.29 (s, 1H), 7.91-7.81 (m, 2H), 7.52-7.30 (m, 8H), 4.91-4.88 and 3.90-3.87 (AB system, J = 10.5 Hz,2H), 3.48(s, 3H).

Example 61

1-Methyl-7-phenyl-5-(4-trifluoromethoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used (4-trifluoromethoxy)phenyl boronic acid. The title compound (13mg) was obtained as a pale yellow solid, (yield = 8%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,54

1H NMR (CDCl3, 300 MHz): δ 7.80-7.70 (m, 3H), 7.58-7.36 (m, 7H), 7.24 (s, 1H), 4.89-4.85 and 3.89-3.86 (AB system, J = 10.5 Hz,2H), 3.47(s, 3H).

Example 63

3-[7-(2-isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Intermediate 9 using the same method described for Example 1 and instead of using benzene boronic acid, we used 2-isopropoxyphenyl boronic acid. The title compound (147mg) was obtained as a white solid, (yield = 86%).

TLC: (AcOEt) : Rf :0,8

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.94-7.92 (m, 2H), 7.72-7.69 (m, 1H), 7.53-7.47 (m, 1H), 7.33-7.29 (m, 1H), 7.16-7.14 (m, 1H), 7.08 (s, 1H), 6.99-6.94 (m, 2H), 6.84 (s, 1H), 4.88-4.85 and 3.92-3.90 (AB system, J = 11 Hz), 4.52-4.40 (sept, 1H), 3.88 (s, 3H), 3.51 (s, 3H), 1.22-1.19 (m, 6H).

Example 64

5-(3,4-Dimethoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3,4-dimethoxyphenyl boronic acid. The title compound (88mg) was obtained as a pale yellow solid, (yield = 59%).

TLC: (AcOEt:) : Rf : 0,56

1H NMR (CDCl3, 200MHz): δ 7.91-7.85 (m, 1H), 7.58-7.26 (m, 8H), 7.05-7.00 (m, 1H), 6.83-6.79 (m,1H), 4.83-4.78 and 3.92-3.87 (AB system, J = 10.5 Hz,2H), 3.97(s, 3H), 3.45(s, 3H).

Example 65

1-Methyl-5-(3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3-nitrophenyl boronic acid. The title compound (60mg) was obtained as a beige solid, (yield = 26%).

TLC: (AcOEt:) : Rf : 0,56

1H NMR (CDCl3, 200MHz): δ 8.53(m, 1H), 8.34-8.30 (m, 1H), 8.10-8.06 (m, 1H), 7.84-7.80 (m, 1H), 7.65-7.28 (m, 8H), 4.95-4.89 and 3.93-3.87 (AB system, J = 10.5 Hz,2H), 3.48(s, 3H).

Example 68

5-(3-Amino-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin -2-one

1-Methyl-5-(3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one Example 65 (40 mg, 0.11 mmole)was dissolved in Methanol/CH_2Cl_2 then Pd/C (10 mg) was added and the flask was stirred over hydrogene atmosphere. The solution was filtered over celite, and the solvent was evaporated. The crude material was chromatographied : eluant : AcOEt/Hexane: 1/1. The title compound (6mg) was obtained as a beige solid, (yield = 16%).

TLC: (AcOEt:) : Rf : 0,10

1H NMR (CDCl3, 200MHz): □ 7.58-7.53 (m, 1H), 7.50-7.14 (m, 9H), 6.96-6.80 (m, 2H), 4.88-4.83 and 3.91-3.86 (AB system, J = 10.5 Hz,2H), 3.48(s, 3H).

Example 69

3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 15 using the same method described for Example 1.

The title compound (85mg) was obtained as a pale beige solid, (yield = 54%).

Rf (AcOEt/CH_2Cl_2 : 1/2) : 0,5

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.96(s, 1H arom), 7.96-7.92 (m, 1H arom), 7.73-7.71 (m, 1H arom), 7.56-7.44 (m, 4H arom), 7.40-7.34 (m, 4H arom), 7.27-7.19 (m, 2H arom), 7.09-7.05 (m, 2H arom), 6.80 (s, 1H arom), 4.88-4.83 and 3.91-3.86 (AB system, J = 10 Hz, CH_2), 3.90 (s, 3H, OCH_3), 3.24 (s, 3H, NCH_3).

Example 70

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 15 using the same method described for Example 1. and instead of using benzene boronic acid, we used 2-methoxy-benzene boronic acid.

The title compound (100mg) was obtained as a grey solid, (yield = 63%).

Rf (AcOEt/CH_2Cl_2 : 1/2) : 0,4

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.07-8.03 (m, 1H arom), 7.99 (s, 1H arom), 7.76-7.73 (m, 1H arom), 7.58-7.54 (m, 1H arom), 7.43-7.17 (m, 6H arom), 7.10-6.91 (m, 4H arom), 6.83 (s, 1H arom), 4.90-4.85 and 3.97-3.93 (AB system, J = 10 Hz, CH_2), 3.77 (s, 3H, OCH_3), 3.28 (s, 3H, NCH_3).

Example 71

3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-bromo-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Intermediate 15 using the same method described for Example 1. and instead of using benzene boronic acid, we used 2-chloro-benzene boronic acid.

The title compound (115mg) was obtained as a yellow solid, (yield = 72%).

Rf (AcOEt/CH_2Cl_2 : 1/2) : 0,4

^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.99 (s, 2H arom), 7.75-7.72 (m, 1H arom), 7.56-7.51 (m, 1H arom), 7.45-7.33 (m, 4H arom), 7.31-7.19 (m, 4H arom), 7.09-7.06 (m, 2H arom), 6.80 (s, 1H arom), 4.90-4.85 and 3.97-3.93 (AB system, J = 10 Hz, CH_2), 3.77 (s, 3H, OCH_3), 3.28 (s, 3H, NCH_3).

Example 75

7-(2,6-Dimethoxy-phenyl)-5-(4-methoxy-phenyl)-1-methyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one

Prepared from 5-chloro-1-methyl-7-(3,5-dimethoxy)-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 4-methoxyphenyl boronic acid.

The title compound (26mg) was obtained as a beige solid, (yield = 15%).

TLC: (AcOEt:) : Rf : 0,13

1H NMR (CDCl3, 300MHz): δ 7.78-7.69 (m, 1H),7.58-7.55 (m, 1H), 7.39-7.27 (m, 4H), 6.92-6.89 (m, 2H), 6.64-6.62 (m, 2H), 4.79-4.76 and 3.94-3.91 (AB system, J = 10.5 Hz,2H), 3.85 (s, 3H), 3.76 (s, 6H), 3.44 (s, 3H).

Example 77

7-(2,6-Dimethoxy-phenyl)-1-methyl-5-(4-methyl-3-nitro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-chloro-1-methyl-7-(3,5-dimethoxy)-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and

instead of using 3-formylbenzene boronic acid, we used (4-methyl-3-nitro-phenyl)-phenyl boronic acid. The title compound (64mg) was obtained as a beige solid, (yield = 33%).

1H NMR (CDCl3, 300MHz): δ 8.27 (s, 1H), 7.98-7.96 (m, 1H),7.60-7.57 (m, 1H), 7.42-7.37 (m, 2H), 7.29-7.26 (m, 2H), 6.64-6.62 (m, 2H), 4.88-4.85 and 3.98-3.94 (AB system, J = 10.5 Hz,2H), 3.74 (s, 6H), 3.48 (s, 3H), 2.64 (s, 3H).

Example 79

5-(3-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

Prepared from 5-Chloro-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one using the same method described for Example 9 and instead of using 3-formylbenzene boronic acid, we used 3-methoxyphenyl boronic acid. The title compound (11mg) was obtained as a yellow solid, (yield = 10%).

TLC: (Hexane/AcOEt: 1/1) : Rf : 0,22

1H NMR (CDCl3, 200 MHz): δ 7.88-7.72 (m, 1H), 7.84-7.29 (m, 9H), 7.19-7.15 (m,, 1H), 7.08-7.02 (m,1H) 4.91-4.86 and 3.92-3.88 (AB system, J = 10.5 Hz,2H), 3.88 (s, 3H), 3.49 (s, 1H).

Example 81

3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-iodo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 11** using the same conditions used to prepare**Example 1** but using 5-chloro,2-methoxyphenyl boronic acid instead of benzene boronic acid. The title compound (85mg) was obtained as a yellow solid, in 55% yield.

Rf ($AcOEt/CH_2Cl_2$: 3/7) : 0,3

^1H NMR ($CDCl_3$, 300 MHz): δ 8.06-8.03 (m, 1H), 7.98 (s, 1H), 7.74-7.70 (m, 2H), 7.58-7.55 (m, 1H), 7.45-7.42 (m, 2H), 7.30-7.22 (m, 3H), 6.91-6.88 (m, 1H), 4.91-4.87 and 3.90-3.86 (AB system, J = 10 Hz, 2H), 3.81 (s, 3H), 3.90 (s, 3H), 3.46 (s, 3H).

Example 82

3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-(7-iodo-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile **Intermediate 11** using the same conditions used to prepare**Example 1** but using 2-chloro,6-methoxyphenyl boronic acid instead of benzene boronic acid. The title compound (115mg) was obtained as a beige solid, in 74% yield.

Rf ($AcOEt/CH_2Cl_2$: 3/7) : 0,3

^1H NMR ($CDCl_3$, 300 MHz): δ 8.10-7.96(m, 1H), 7.75-7.73 (m, 1H), 7.59-7.44 (m, 3H), 7.30-7.20 (m, 3H), 7.10-7.07 (m, 1H), 6.89-6.86 (m, 1H), 4.91-4.87 and 3.90-3.86 (AB system, J = 10 Hz, 2H), 3.81 (s, 3H), 3.90 (s, 3H), 3.46 (s, 3H).

Preparation of examples of general formula I (Scheme 6)

Example 19

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

To a solution of compound 3-(8-methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl)-benzonitrile Example 1 (46 mg, 0.12 mmol) in absolute ethanol (2 ml), were added dropwise H_2O_2 aqueous (30% wt in water, 42 µl), followed by aqueous NaOH (0.5 M, 60 µl). The solution was stirred at RT for 16 hours. Removal of ethanol in vacuum gave the crude material which was purified by silica gel column chromatography with CH_2Cl_2/MeOH: 95/5 to give after crystallization from ether/pentane the title compound (27mg) as a white solid, (yield = 72%).

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

mp 191-192°C

HPLC 99.2%

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.14 (m, 1H), 7.91-7.95 (m, 1H), 7.78-7.83 (m, 1H), 7.53-7. 45 (m, 1H), 7.34-7.41 (m, 5H), 7.19 (s, 1H), 6.87 (s, 1H), 6.12 and 5.69 (2 s-broad, 2H), 4.88-4.83 and 3.93-3.87 (AB system, J = 10 Hz_2), 3.94 (s, 3H), 3.50 (s, 3H).

Example 20

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzamide

Prepared from 3-[7-(4-fluorophenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 2 using the same method described for Example 19. The title compound (35mg) was obtained as a white solid, (yield = 78%).

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.14 (m, 1H), 7.94-7.90 (m, 1H), 7.82-7.79 (m, 1H), 7.53-7.36 (m, 3H), 7.16 (s, 1H), 7.11-7.02 (s, 2H), 6.87 (s, 1H), 6.20 and 5.73 (2 s-broad, 2H), 4.88-4.83 and 3.91-3.86 (AB system, J = 11 Hz_2), 3.94 (s, 3H), 3.49 (s, 3H).

Example 21

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzamide

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 3 using the same method described for Example 19. The title compound (50mg) was obtained as a white solid, yield = 83%.

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (m, 1H), 7.95-7.92 (m, 1H), 7.85-7.82 (m, 1H), 7.51-7.46 (m, 1H), 7.35-7.29 (s, 1H), 7.21-7.17 (s, 2H), 7.00-6.94 (m, 2H), 6.86 (s, 1H), 6.16 and 5.63 (2 s-broad, 2H), 4.86-4.82 and 3.95-3.91 (AB system, J = 11 Hz_2), 3.89 (s, 3H), 3.76 (s, 3H), 3.50 (s, 3H).

Example 22

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[8-methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 4 using the same method described for Example 19. The title compound (47mg) was obtained as a white solid, yield = 71%.
TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2
^1H NMR ($CDCl_3$, 200 MHz): δ 8.14 (m, 1H), 7.95-7.91 (m, 1H), 7.85-7.78 (m, 1H), 7.55-7.45 (m, 1H), 7.39-7.35 (m, 2H), 7.16 (s, 1H), 6.94-6.89 (m, 2H), 6.85 (s, 1H), 6.24 and 5.65 (2 s-broad, 2H), 4.87-4.82 and 3.92-3.87 (AB system, J = 11 Hz_2), 3.94 (s, 3H), 3.82 (s, 3H), 3.49 (s, 3H).

Example 23

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 5 using the same method described for Example 19. The title compound (74mg) was obtained as a white solid, yield = 84%.
TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2
^1H NMR ($CDCl_3$, 300 MHz): δ 8.09 (m, 1H), 7.95-7.92 (m, 1H), 7.87-7.84 (m, 1H), 7.71-7.65 (m, 1H), 7.56-7.42 (m, 3H), 7.30-7.28 (m, 1H), 7.12 (s, 1H), 6.87 (s, 1H), 6.17 and 5.65 (2 s-broad, 2H), 4.88-4.85 and 3.94-3.90 (AB system, J = 11 Hz_2), 3.90 (s, 3H), 3.51 (s, 3H).

Example 24

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 6 using the same method described for Example 19. The title compound (30mg)was obtained as a white solid, yield = 64%.

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.13 (m, 1H), 7.94-7.90 (m, 1H), 7.82-7.79 (m, 1H), 7.54-7.44 (m, 2H), 7.30 (m, 3H), 7.17 (s, 1H), 6.87 (s, 1H), 6.15 and 5.70 (2 s-broad, 2H), 4.89-4.84 and 3.91-3.85 (AB system, J = 11 Hz_2), 3.95 (s, 3H), 3.49 (s, 3H).

Example 25

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 7 using the same method described for Example 19. The title compound (22mg) was obtained as a white solid, yield = 64%.

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

^{1}H NMR (CDCl3, 200 MHζ): δ 8.14 (m, 1H), 7.94-7.78 (m, 2H), 7.53-7.45 (m, 1H), 7.35 (m, 4H), 7.16 (s, 1H), 6.87 (s, 1H), 6.20 and 5.75 (2 s-broad, 2H), 4.88-4.83 and 3.91-3.86 (AB system, J = 11 Hz_2), 3.94 (s, 3H), 3.49 (s, 3H).

Example 26

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

Prepared from 3-(7-furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Example 8 using the same method described for Example 19. The title compound (12mg) was obtained as a white solid, yield = 46%.

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,2

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (m, 1H), 7.93-7.95 (m, 1H), 7.77-7.80 (m, 1H), 7.47-7.53 (m, 1H), 7.19-7.22 (d, J = 9 Hz, 1H), 6.84-6.85 (d, J = 2 Hz, 1H), 6.75-6.80 (dd, J = 2 Hz and 9 Hz, 1H), 5.64 and 6.20 (2 s-broad, 2H), 3.80-3.84 and 4.79-4.83 (AB system, J = 10 Hz_2), 3.91 (s, 3H), 3.43 (s, 3H).

Example 27

3-(1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

Prepared from 3-(1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Example 11 using the same method described for Example 19. The title compound (26mg) was obtained as a yellow solid, yield = 70%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.18 (s, 1H), 7.97-7.94 (m, 1H), 7.83-7.78 (m, 2H), 7.54-7.35 (m, 8H), 6.19 and 5.58 (2 s-broad, 2H), 4.90-4.84 and 3.91-3.86 (AB system, J = 10 Hz_2), 3.47 (s, 3H).

Example 28

3-[7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile Example 12 using the same method described for Example 19. The title compound (32mg) was obtained as a yellow solid, yield = 80%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H), 7.98-7.96 (m, 1H), 7.86-7.83 (m, 1H), 7.76-7.73 (m, 1H), 7.50-7.40 (m, 3H), 7.27-7.24 (m, 2H), 7.01-6.97 (m, 2H), 6.25 and 5.21 (2 s-broad, 2H), 4.87-4.84 and 3.93-3.89 (AB system, J = 10 Hz_2), 3.77 (s, 3H), 3.47 (s, 3H).

Example 29

3-[7-(3-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(3-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile Example 13 using the same method described for Example 19. The title compound (50mg) was obtained as a yellow solid, yield = 80%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.19 (m, 1H), 7.94-7.92 (m, 1H), 7.81-7.76 (m, 2H), 7.54-7.34 (m, 4H), 7.08-6.92 (m, 3H), 6.28 and 5.22 (2 s-broad, 2H), 4.90-4.85 and 3.91-3.85 (AB system, J = 10 Hz_2), 3.85 (s, 3H), 3.47 (s, 3H).

Example 30

3-[7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile Example 14 using the same method described for Example 19. The title compound (37mg) was obtained as a yellow solid, yield = 71%.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H), 7.97-7.94 (m, 1H), 7.81-7.73 (m, 2H), 7.52-7.40 (m, 5H), 6.96-6.94 (m, 2H), 6.23 and 5.24 (2 s-broad, 2H), 4.88-4.85 and 3.90-3.86 (AB system, J = 10 Hz_2), 3.84 (s, 3H), 3.46 (s, 3H).

Example 31

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2,5-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 9 using the same method described for Example 19. The title compound (50mg) was obtained as a yellow solid, yield = 80%.
^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H, 7.98-7.96 (m, 1H), 7.88-7.85 (m, 1H), 7.76-7.72 (m, 1H), 7.53-7.39 (m, 3H), 6.88-6.83 (m, 3H), 6.01 and 5.71 (2 s-broad, 2H), 4.88-4.84 and 3.93-3.89 (AB system, J = 11 Hz_2), 3.78 (s, 3H), 3.71 (s, 3H), 3.47 (s, 3H).

Example 32

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2,6-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile Example 16 using the same method described for Example 19. The title compound (82mg) was obtained as a yellow solid, yield = 87%.

1H NMR ($CDCl_3$, 300 MHz): δ 8.17 (m, 1H), 7.98-7.95 (m, 1H), 7.87-7.85 (m, 1H), 7.60-7.57 (m, 1H), 7.51-7.48 (m, 1H), 7.40-7.37 (m, 1H), 7.30-7.24 (m, 2H), 6.64-6.61 (m, 2H), 6.17 and 5.76 (2 s-broad, 2H), 4.86-4.83 and 3.98-3.94 (AB system, J = 11 Hz_2), 3.81 (s, 6H), 3.48 (s, 3H).

Example 33

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2,4-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile Example 17 using the same method described for Example 19. The title compound (45mg) was obtained as a yellow solid, yield = 72%.

1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H), 7.98-7.95 (m, 1H), 7.87-7.84 (m, 1H), 7.72-7.69 (m, 1H), 7.52-7.49 (m, 1H), 7.44-7.38 (m, 2H), 7.19-7.16 (m, 1H), 6.55-6.53 (m, 2H), 6.17 and 5.66 (2 s-broad, 2H), 4.87-4.83 and 3.92-3.88 (AB system, J = 11 Hz_2), 3.83 (s, 3H), 3.75 (s, 3H), 3.46 (s, 3H).

Example 34

3-[8-Methoxy-7-(4-benzamide)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-(8-Methoxy-1-methyl-2-oxo-7-(4-cyanophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile Example 43 using the same method described for Example 19. The title compound (13mg)was obtained as a white solid, yield = 80%.

^1H NMR (DMSO-d6, 200 MHz): δ 8.11-7.37 (m, 12H), 7.26 (s, 1H), 7.15 (s, 1H), 4.67-4.61 and 3.92-3.86 (AB system, J = 12 Hz), 3.97 (s, 3H), 3.45 (s, 3H).

Example 36

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 10 using the same method described for Example 19. The title compound (45mg) was obtained as a pale yellow solid, yield = 85%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.25 (s-broad, 1H), 8.06 (m, 1H), 7.97-7.94 (m, 1H), 7.78-7.75 (m, 1H), 7.51-7.46 (m, 1H), 7.32-7.29 (m, 1H), 7.19-7.17 (m, 2H), 6.99-6.93 (m, 2H), 6.63 (s, 1H), 6.24 and 5.69 (2 s-broad, 2H), 4.41 (s-broad, 2H), 3.85 (s, 3H), 3.74 (s, 3H).

Example 44

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 39 using the same method described for Example 19. The title compound (23mg) was obtained as a white solid, yield = 23%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.00-7.93 (m, 2H), 7.69-7.65 (m, 1H), 7.50-7.43 (m, 1H), 7.32-7.29 (m, 1H), 7.22 (m, 5H), 7.17-7.09 (m, 2H) 6.98-6.94 (m, 2H), 6.89 (s, 1H), 6.11 and 5.55 (2 s-broad, 2H), 5.38-5.31 and 5.14-5.07 (AB system, J = 16 Hz, 2H), 4.96-4.90 and 4.08-4.09 (AB system, J = 10 Hz, 2H), 3.69 (s, 6H).

Example 45

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile using the same method described for Example 37. The title compound (62mg) was obtained as a white solid, yield = 82%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15 (s, 1H), 7.98-7.94 (m, 2H), 7.78-7.76 (m, 1H), 7.51-7.46 (m, 1H), 7.35-7.30 (m, 1H), 7.23-7.20 (m, 1H), 7.16 (s, 1H), 7.00-6.92 (m, 3H), 6.21 and 5.62 (2 s-broad, 2H), 4.83-4.79 and 3.94-3.91 (AB system, J = 10 Hz, 2H), 3.88 (s, 3H), 3.76 (s, 3H), 4.38-4.28 and 3.73-3.63 (AB system, 2H), 1.72-1.64 (m, 2H), 0.86-0.81 (s, 3H).

Example 46

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile using the same method described for Example 38. The title compound (58mg) was obtained as a white solid, yield = 52%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (m, 1H), 8.00-7.95 (m, 1H), 7.73-7.71 (m, 1H), 7.50-7.44 (m, 1H), 7.34-7.29 (m, 1H), 7.19-7.14 (m, 7H), 7.00-6.93 (m, 2H), 6.79 (s, 1H), 6.17 and 5.61 (2 s-broad, 2H), 4.52-4.43 and 4.08-3.98 (AB system, 2H), 4.85-4.81 and 3.94-3.91 (AB system, J = 11 Hz, 2H), 3.79 (s, 3H), 3.75 (s, 3H), 3.05-3.00 (t, 2H).

Example 47

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile using the same method described for Example 35. The title compound (37mg) was obtained as a white solid, yield = 59%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.16 (m, 1H), 8.98-7.94 (m, 1H), 7.79-7.75 (m, 1H), 7.52-7.44 (m, 1H), 7.36-7.28 (m, 1H), 7.25-7.20 (m, 1H), 7.17 (s, 1H), 7.01-6.93 (m, 3H), 6.23 and 5.62 (2 s-broad, 2H), 4.83-4.78 and 3.95-3.90 (AB system, J = 10 Hz), 3.88 (s, 3H), 3.76 (s, 3H), 4.43-4.28 and 3.81-3.64 (AB system, 2H), 1.62(m 2H), 1.29-1.18 (m, 6H), 0.81-0.76 (s, 3H).

Example 49

3-[7-(4-Acetylphenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(4-acetylphenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 48 using the same method described for Example 35. The title compound (24mg) was obtained as a white solid, yield = 38%.

TLC: (CH_2Cl_2/MeOH: 9/1) : Rf : 0,4

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.15 (m, 1H), 7.98-7.90 (m, 3H), 7.83-7.81 (m, 1H), 7.55-7.47 (m, 3H), 7.04 (s, 1H), 6.89 (s, 1H), 6.23 and 5.67 (2 s-broad, 2H), 4.89-4.85 and 3.91-3.88 (AB system, J = 10 Hz), 3.95 (s, 3H), 3.50 (s, 3H), 2.61 (s, 3H).

Example 54

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(3,4-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile **Example 53** using the same conditions used to prepare **Example 19**. The title compound (45mg) was obtained as a yellow solid, yield = 86%.

1H NMR ($CDCl_3$, 300 MHz): δ 8.20 (m, 1H), 7.95-7.93 (m, 1H), 7.82-7.74 (m, 2H), 7.54-7.40 (m, 3H), 6.93-6.91 (m, 3H), 6.27 and 5.76 (2 large s, 2H), 4.88-4.84 and 3.90-3.86 (AB system, J = 11 Hz, 2H), 3.90 (s, 6H), 3.46 (s, 3H).

Example 72

3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

Prepared from 3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile **Example 69** using the same method described for Example 35. The title compound (35mg) was obtained as a yellow solid, yield = 67%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.19 (s, 1H), 7.95-7.92 (m, 1H), 7.83-7.81 (m, 1H), 7.53-7.49 (m, 3H), 7.41-7.33 (m, 6H), 7.21-7.19 (m, 1H), 7.10-7.07 (m, 2H), 6.81 (s, 1H), 6.31 and 5.83 (2 large s, 2H), 4.86-4.83 and 3.92-3.89 (AB system, J = 10 Hz, 2H), 3.26 (s, 3H).

Example 73

3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2-chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile **Example 71** using the same method described for Example 35. The title compound (35mg) was obtained as a yellow solid, yield = 67%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.18 (s, 1), 7.97-7.84 (m, 2H), 7.52-7.49 (m, 1H), 7.40-7.23 (m, 5H), 7.18-7.06 (m, 3H), 6.97-6.88 (m, 2H), 6.80 (s, 1H), 6.33 and 5.82 (2 large s, 2H), 4.85-4.82 and 3.96-3.92 (AB system, J = 10 Hz, 2H), 3.71 (s, 3H), 3.27 (s, 3H).

Example 74

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2-methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile **Example 70** using the same method described for Example 35. The title compound (60mg) was obtained as a yellow solid, yield = 83%.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.14 (s, 1H), 7.95-7.87 (m, 2H), 7.53-7.50 (m, 1H), 7.43-7.20 (m, 4H), 7.27-7.17 (m, 4H), 7.09-7.06 (m, 2H), 6.78 (s, 1H), 6.25 and 5.77 (2 large s, 2H), 4.87-4.84 and 3.94-3.91 (AB system, J = 10 Hz, 2H), 3.27 (s, 3H).

Example 78

3-[7-(2-Isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

Prepared from 3-[7-(2-isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile **Example 63** using the same method described for Example 35. The title compound (89mg) was obtained as a white solid, yield = 69%.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.12 (m, 1H), 7.95-7.91 (m, 1H), 7.81-7.77 (m, 1H), 7.51-7.44 (m, 1H), 7.33-7.29 (m, 1H), 7.17-7.12 (m, 2H), 6.98-6.91 (m, 2H), 6.84 (s, 1H), 6.09 and 5.62 (2 s-broad, 2H), 4.87-4.82 and 3.94-3.89 (AB system, J = 11 Hz), 4.50-4.41 (sept, 1H), 3.88 (s, 3H), 3.51 (s, 3H), 1.20-1.17 (m, 6H).

Example 83

3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]- benzamide

Prepared from 3-[7-(5-chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile **Example 81** using the same conditions used to prepare **Example 19**. The title compound (37mg) was obtained as a yellow solid, yield = 79%.

1H NMR ($CDCl_3$, 300 MHz): δ 8.18 (m, 1H), 7.99-7.97 (m, 1H), 7.85-7.83 (m, 1H), 7.73-7.69 (m, 1H), 7.52-7.41 (m, 3H), 7.29-7.23 (m, 2H), 6.90-6.87 (m, 1H), 6.26 and 5.59 (2 large s, 2H), 4.89-4.85 and 3.91-3.8 (AB system, J = 11 Hz, 2H), 3.76 (s, 3H), 3.48 (s, 3H).

Example 84

3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]- benzamide

Prepared from 3-[7-(2-chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile **Example 82** using the same conditions used to prepare **Example 19**. The title compound (48mg) was obtained as a beige solid, yield = 77%.

1H NMR ($CDCl_3$, 300 MHz): δ 8.12 (m, 1H), 7.97-7.95 (m, 1H), 7.89-7.87 (m, 1H), 7.52-7.42 (m, 2H), 7.28-7.23 (m, 3H), 7.09-7.06 (m, 1H), 6.88-6.85 (m, 1H), 6.31 and 5.61 (2 large s, 2H), 4.90-4.86 and 3.98-3.94 (AB system, J = 11 Hz, 2H), 3.74 (s, 3H), 3.49 (s, 3H).

Preparation of examples of general formula I (Scheme 4)

Example 35

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

To a mixture of toluene (6 mL) and Aliquat 336 (2 μL) was introduced hexyl bromine (70 μL, 0.499 mmole) while the mixture was agitated, powdered 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Example 10 (100 mg, 0.25 mmole) and 50% aqueous sodium hydroxide (0.27 mL) were added to the reaction mixture. The two-phase system was stirred vigorously for 4 hours. The phases were separated, and the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic extracts were washed with cold water (10 mL); then the organic phase were dried over Na_2SO_4 and concentrated to dryness. The title compound was crystallised from Et_2O/Pentane to afford 80mg of a white powder - yield: 66%.

TLC: (CH_2Cl_2/Et_2O: 1/1) : Rf :0,8

^1H NMR ($CDCl_3$, 300 MHz): δ 8.04-7.93 (m, 2H), 7.74-7.71 (m, 1H), 7.52-7.49 (m, 1H), 7.36-7.31 (m, 1H), 7.23-7.20 (m, 1H), 7.13 (s, 1H), 7.02-6.96 (m, 2H), 6.94 (s, 1H), 4.84-4.81 and 3.93-3.90 (AB system, J = 10 Hz), 3.88 (s, 3H), 3.81 (s, 3H), 4.42-4.33 and 3.74-3.65 (AB system, 2H), 1.57 (m 2H), 1.18 (m, 6H), 0.81-0.76 (s, 3H).

Example 37

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 10 using the same method described for **Example 35** using propyl iodide instead of hexyl bromine,. The title compound (99mg) was obtained as a white solid, yield = 89%.

TLC: (CH_2Cl_2/Et_2O: 1/1) : Rf :0,7

^1H NMR ($CDCl_3$, 200 MHz): δ 8.04-7.93 (m, 2H), 7.74-7.71 (m, 1H), 7.56-7.48 (m, 1H), 7.38-7.30 (m, 1H), 7.23-7.20 (m, 1H), 7.12 (s, 1H), 7.02-6.96 (m, 2H), 6.94 (s, 1H), 4.86-4.81 and 3.93-3.90 (AB system, J = 10 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 4.42-4.32 and 3.74-3.65 (AB system, 2H), 1.60 (m, 2H), 0.86-0.79 (s, 3H).

Example 38

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 10 using the same method described for Example 35 using phenethyl bromine instead of hexyl bromine. The title compound (110mg) was obtained as a white solid (yield = 87%).

TLC: (CH_2Cl_2/Et_2O: 1/1) : Rf :0,8

^1H NMR ($CDCl_3$, 200 MHz): δ 7.96-7.92 (m, 1H), 7.72-7.70 (m, 2H), 7.53-7.45 (m, 1H), 7.37-7.29 (m, 1H), 7.20-7.15 (m, 6H), 7.06 (s, 1H), 7.01-6.94 (m, 2H), 6.82 (s, 1H), 4.59-4.49 and 4.09-3.99 (AB system, 2H), 4.87-4.82 and 3.93-3.88 (AB system, J = 9 Hz, 2H), 3.88 (s, 3H), 3.80 (s, 3H), 3.05-2.98 (t, 2H).

Example 39

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 10 using the same method described for Example 35 using benzyl bromine instead of hexyl bromine. The title compound (95mg) was obtained as a yellow solid (yield = 90%).

TLC: (CH_2Cl_2/Et_2O: 1/1) : Rf :0,8

^1H NMR ($CDCl_3$, 200 MHz): δ 7.89-7.85 (m, 1H), 7.73-7.67 (m, 2H), 7.53-7.49 (m, 1H), 7.30-7.20 (m, 5H), 7.03-6.91 (m, 2H), 5.39-5.31 and 5.11-5.03 (AB system, J = 10 Hz, 2H), 4.97-4.92 and 4.07-4.02 (AB system, J = 10 Hz, 2H), 3.75 (s, 3H), 3.70 (s, 3H).

Preparation of examples of general formula I (Scheme 4)

Example 66

5-(3-Hex-1-ynyl-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one

To 10 mL of degazed acetonitrile were added 5-(3-bromo-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one **Example 62** (200 mg, 0.46 mmol),

phenylacetylene (715 µL, 2.30 mmol), copper iodide (15 mg, 0.08 mmol), triphenylphosphine (30 mg, 0.11 mmol), $PdCl_2$ (10 mg, 0.06 mmol) and triethylamine (0.9 mL). The mixture was stirred for 16 hours at 50°C under nitrogene atmosphere. The working solution was evaporated under vacuum. The residue was partitioned from water and ethyl acetate and extracted two more times with ethyl acetate. The organic phase was dried over Na_2SO_4 and concentrated until dryness. The residue was purified by chromatography (eluant : Hexane/EtOAc: 1/1). The title compound was crystallised from ether/pentane to afford 134 mg of the title compound: beige solid, yield = 90%.
1H NMR (CDCl3, 200 MHz): δ 7.67-7.21 (m, 10H), 6.84 (s, 1H), 4.85-4.80 and 3.92-3.88 (AB system, J = 10.5 Hz,2H), 3.92(s, 3H), 3.47 (s, 3H), 2.38-2.34 (m, 2H), 1.60-1.42 (m, 4H), 0.96-0.89 (m, 3H).

Prepared from 3-[8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile Example 10 using the same method described for Example 35 using benzyl bromide instead of hexyl bromide. The title compound (95mg) was obtained as a yellow solid, (yield = 90%).

Example 67

{3-[3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-phenyl]-prop-2-ynyl}-carbamic acid tert-butyl ester

Prepared from 5-(3-bromo-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one **Example 62** using the same method described for Example 35 using propargyl Boc-amine instead of hex-1-yne . The title compound (51mg) was obtained as a beige solid, (yield = 22%).
TLC: (Hexane/AcOEt: 1/1) : Rf : 0.17
1H NMR (CDCl3, 300 MHz): δ 7.69-7.28 (m, 9H), 7.20 (s, 1H), 6.86 (s,1H), 4.86-4.82 and 3.89-3.868 (AB system, J = 10.5 Hz,2H), 4.82 (broad s, 1H), 4.14-4.13 (m, 2H), 3.94(s, 3H), 3.49 (s, 3H), 1.47 (s, 9H).

EXAMPLE B

PHARMACOLOGICAL ACTIVITY : INHIBITION OF PHOSPHODIESTERASES.

Isolation of phosphodiesterases from smooth muscle

3 g of tunica media from bovine aorta was cut in small piece and homogenized in a glass potter with 7 volumes/weight of buffer A containing protease inhibitors cocktails (20 mM Tris-HCl, 0.25 M saccharose, 2mM magnesium acetate, 1mM dithiothreitol, 5 mM EGTA, 2000 U/ml aprotinine, 10 mg/l leupeptine, 10 mg/l of soybean chemotrypsin inhibitor). The homogenate was centrifuged at 875000 g for 1 h and the surpernant was then transferred in DEAE-Sephacel (15 X 1.6 cm). The column was equilibrated beforehand with a buffer B (buffer A without saccharose, d'EGTA and protease inhibitors). The column was washed until no absorption was detected at 280 nm and then eluated with linear gradient of NaCl (0-0.5 M) in the buffer B. Fractions of 3 ml volume were collected and the enzymatic activities were assessed under the conditions described below in order to identify fractions containing PDE1, PDE3, PDE4 and PDE5 (Lugnier et al., Biochem. Phamacol., 35 (1986) 1746-1751). Fractions were aliquoted and stored at -80°C until further use. PDE2 was prepared from bovine endothelial cells using the same procedure (Lugnier and Schini, Biochem. Pharmacol. 1990, 39; 75-84).

Protocol for the measurement of phosphodiesterase activities

Cyclic nucleotide phosphodiesterase activity was determined by radioenzymatic assay using tritiated cyclic AMP or GMP (1 µM) as a substrate (Lugnier et el., 1986). The monophosphated adenosine or guanosine released by the hydrolysis of tritiated cyclic nucleotides was transformed into tritiated adenosine or guanosine by excess of nucleotidase. The obtained nucleoside was separated from nucleotides by anion exchange chromatography. Nucleoside radioactivity was determined by liquid scintillation. All enzymatic reactions were conducted in duplicates and under conditions to obtain less than 15% of substrate hydrolysis.

Measurement of PDE2 inhibition.

The concentration of substance required to inhibit 50% of the enzymatic activity (IC_{50}) in the presence of 1 μM cyclic AMP was determined by non-linear regression analysis of the rate of hydrolysis (Prism, GraphPad).

Selectivity

The phosphodiesterase inhibitory activity of compounds was evaluated on other isoforms of phosphodiesterases such as PDE3, and PDE4 of vascular smooth muscle.

Obtained results were presented in Tables 1 and 2, showing the percentage of PDE inhibition by 10 μM of test compound or the inhibitory concentration at which the enzymatic activity is reduced by 50% (IC50).

Table 1

Inhibitory activity of representative compounds of formula (I) on PDE2.

Examples	PDE2 percentage of inhibition at 10μM or [IC_{50} (μM)]	Examples	PDE2 percentage of inhibition at 10μM or [IC_{50} (μM)]
1	83% [0.57]	43	92%
2	97% [0.6]	44	88%
3	100%	45	48%
4	97% [0.3]	46	78%
5	98%	47	59%
6	96% [1.4]	48	97%
7	91% [1.2]	49	99%
8	47%	50	95% [0.3]
9	84%	51	28%
10	94%	52	78%
11	79% [2.2]	53	95%
12	40%	54	94%
13	91%	55	53%
14	92%	56	70%
15	98%	57	74%
16	100% [0.6]	58	91%
17	98%	59	43%
18	27%	60	88%
19	97% [0.05]	61	31%
20	99% [0.2]	62	98%
21	98% [0.04]	63	98%
22	99% [0.026]	64	79%
23	95% [0.06]	65	
24	98% [0.1]	66	
25	97% [0.12]	67	
26	71%	68	
27	96% [1.1]	69	
28	97%	70	
29	95%	71	
30	95%	72	
31	99% [0.1]	73	
32	100% [0.03]	74	
33	99%	75	
34	98%	76	
35	39%	77	
36	94% [0.5]	78	
37	45%	79	

38	86% [4.0]	80	
39	72%	81	
40		82	
41		83	
42	1%	84	

Table 2

Inhibitory activity of selected compounds of formula (I) on PDE2, PDE3 .and PDE4

Examples	IC_{50} (μM) or percentage Of inhibition at 10μM		
	PDE2	PDE3	PDE4
19	97% [0.05]	23%	14%
21	98% [0.04]	9%	18%
22	99% [0.026]	22%	50%
23	95% [0.06]	25%	20%
31	99% [0.1]	0%	25%
32	100% [0.03]	0%	27%

Overall, most of tested compounds showed a marked inhibitory activity on PDE2. Preferred molecules showed a good profile of potency and selectivity towards PDE2, as these compounds show a very weak inhibitory activity on the other PDE isoforms, especially on the PDE3.

EXAMPLE C

BEHAVIOURAL TESTS

Swim test

This test is based on the induction of alternative behaviour in rodents subjected to an acute stress. In this model, the rat or mouse placed in a container filled with water show periods of increased swimming activity and periods of relative immobility. Clinically active anti-depressants have been found to delay the onset of the first phase of immobility and to reduce the total time of relative immobility.

Swiss mice were used. The animal was placed individually in the water where it remained for 6 minutes. The animal was given an accommodation period of 2 minutes. During the last 4 minutes observation period, the onset of the first period of immobility and the duration of the periods of immobility were recorded.

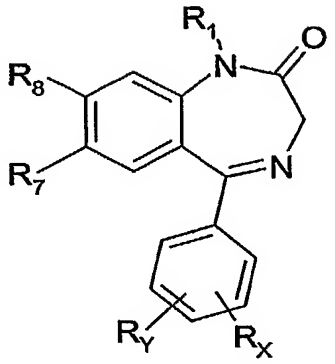
Treatment was conducted 20 minutes prior the test. Animals were randomly distributed in 4 groups. Control group received the vehicle whereas the other 3 groups received different single dose of test compound.

Results are illustrated in figure 1 : Mean Duration of Phases of Immobility (s) ; N= 10; $p<0,005$ (Dunnett's test).

Statistical analyses revealed a significant difference between groups regarding the period of total immobility ($p = 0.005$). Mice treated with 0.3, 3 or 30 mg/kg of test compound showed significantly shorter time of relative immobility than control animals.

CLAIMS

1. Compounds of general formula (I) :



(I)

wherein :

. R_1 represents an hydrogen atom, (C_1-C_6) alkyl, aryl, (C_1-C_6)alkylaryl, aryl(C_1-C_6)alkyl group, (C_3-C_6) alkenyl, or (C_3-C_6) alkenylaryl,

. R_7 represents a, substituted or not substituted, aryl or heteroaryl group,

when R_7 is a substituted aryl, it is preferably mono or bis substituted by the following groups : a (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, (C_3-C_6)alkenyloxy, acyl, halogen, trifluoromethyl, difluoromethyl, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkylaryl, aryl, or $-CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen atom, an (C_1-C_6)alkyl group, (C_3-C_6)alkenyl group, an alkylaryl, an alkenylaryl, and an aryl group,

. R_8 represents a hydrogen atom or a OR_{10} group, wherein R_{10} is a hydrogen atom, an (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6) alkenyl, an (C_3-C_6)alkenylaryl, aryl, or heterocyclic group, aromatic or not, having 1 to 3 heteroatoms chosen between O, N, S,

when R_{10} is an aryl, it is preferably mono or bis substituted by the following groups : an hydrogen, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, (C_3-C_6)alkenyloxy, halogen, trifluoromethyl, difluoromethyl, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkylaryl, aryl, and $-CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen

atom, an (C_1-C_6)alkyl group, (C_3-C_6)alkenyl group, an alkylaryl, an alkenylaryl, and an aryl group,

. R_X represents an hydrogen atom, an halogen atom, a methyl, a methoxy, an acetyl, a trifluoromethyl, CN, COH or $CONH_2$ group,

. R_Y represents an hydrogen, halogen atom, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, aryl, (C_3-C_6)cycloalkyloxy, (C_1-C_6)alkyloxy, alkenyl, (C_3-C_8)alkenyloxy, alkynyl, alkynyloxy, acyl, halogen, trifluoromethyl, difluoromethyl, trifluoromethoxy, difluoromethoxy, cyano, nitro, hydroxy, carboxamide, amino, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, $NHCOR_{12}$ where R_{12} is a (C_1-C_6)alkyl, (C_1-C_6)alkyloxy, hydroxy, (C_1-C_6)alkylaryl, aryl, or -$CONR_{13}R_{14}$ wherein R_{13} and R_{14}, independently from each other, are selected from the group consisting of a hydrogen atom, an (C_1-C_6)alkyl group, an (C_2-C_6)alkenyl group, an alkynyl, an alkylaryl, an alkenylaryl, an alkynylaryl, and an aryl group,
with the proviso that when R_8 is an hydrogen atom, then R_X or R_Y is different from hydrogen,
with the further proviso that when R_X or R_Y is halogen, it is not on position 2 of the phenyl,
or a pharmaceutically acceptable salt thereof.

2. Compounds of formula (I) according to claim 1, wherein R_8 is an hydrogen atom, a methoxy, ethoxy or phenoxy group.

3. Compounds of formula (I) according to one of the preceding claims, wherein at least one of R_X and R_Y is different from hydrogen.

4. Compounds of formula (I) according to one of the preceding claims, wherein R_Y is an hydrogen atom and R_X is different from hydrogen.

5. Compounds of formula (I) according to one of the preceding claims, wherein one of R_X and R_Y, different from hydrogen, is on position 3 of the phenyl group represented in formula (I).

6. Compounds of formula (I) according to one of the preceding claims, wherein R_X, different from hydrogen, is on position 3 of the phenyl group represented in formula (I).

7. Compounds of formula (I) according to one of the preceding claims, wherein R_X represents $CONH_2$ or CN group.

8. Compounds of formula (I) according to any one of the preceding claims, wherein R_Y represents H, an halogen atom, CF_3, (C_1-C_6)aminoalkyl, (C_1-C_6)aminodialkyl, -$NHCOR_{12}$, -$CONH_2$, a (C_1-C_6)alkyloxy group or a (C_1-C_6)alkyl group, preferably hydrogen.

9. Compounds of formula (I) according to any one of claims 1 to 8, wherein R_1 represents an alkyl group, preferably methyl, ethyl, or propyl, an alkenyl group, preferably propenyl, or arylalkyl group.

10. Compounds of formula (I) according to any one of claims 1 to 9, wherein R_7 is a furan group, said group is preferably a furan-2-yl.

11. Compounds of formula (I) according to any one of claims 1 to 9, wherein R_7 is an unsubstituted aryl group, preferably unsubstituted phenyl group.

12. Compounds of formula (I) according to any one of claims 1 to 9, wherein R_7 is a substituted aryl or heteroaryl group, preferably a substituted phenyl group.

13. Compounds of formula (I) according to claim 12, wherein said substituted aryl or heteroaryl group is substituted with one or two, identical or different, substituents selected in the group consisting of halogen, amino, aminoacyl, (C_1-C_6)alkyl and (C_1-C_6)alkyloxy..

14. Compounds of formula (I) according to claim 13, wherein alkoxy is a methoxy or ethoxy group.

15. Compounds of formula (I) according to claim 13, wherein the substituted aryl is a phenyl group selected in the group consisting of 4-methoxy-phenyl, 4-fluoro-phenyl, 2-methoxy-phenyl, 2-chloro-phenyl, 4-chloro-phenyl, 3-chloro-phenyl, 3-methoxy-phenyl, 2,5-dimethoxy-phenyl, 2,6-dimethoxy-phenyl, 4-benzamide, 4-cyanophenyl, 2,4-dimethoxy-phenyl, 4-carboxamide-phenyl, 4-acetyl-phenyl, 2-isopropoxy-phenyl, and 3,4-dimethoxy-phenyl groups.

16. Compounds selected in the group consisting of :

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4] diazepin-5-yl]-benzonitrile

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(3-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(4-Methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

8-Ethoxy-1-ethyl-5,7-diphenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[7-(4-Fluoro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(3-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-(7-Furan-2-yl-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-(1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(3-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,5-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,6-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-(1-Methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzaldehyde

3-(8-Methoxy-7-(4-benzamide)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

5-(3-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(2-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[8-Methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2-Chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(4-Chloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(8-Methoxy-1-methyl-2-oxo-7-(4-cyanophenyl)-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

5-(3-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[1-Benzyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-propyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[8-Methoxy-7-(2-methoxy-phenyl)-2-oxo-1-phenethyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[1-Hexyl-8-methoxy-7-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(4-Acetyl-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(4-Acetyl-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(4-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(2-Methoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-(7-Furan-2-yl-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(3,4-Dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(3,5-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3,4-Dichloro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(4-Fluoro-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Acetyl-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-7-phenyl-5-(3-trifluoromethyl-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-5-(4-methyl-3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-7-phenyl-5-(4-trifluoromethoxy-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Bromo-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

3-[7-(2-Isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Isopropoxy-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

5-(3,4-Dimethoxy-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

7-(2,6-Dimethoxy-phenyl)-5-(4-methoxy-phenyl)-1-methyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

8-Methoxy-5-(4-methoxy-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

7-(2,6-Dimethoxy-phenyl)-1-methyl-5-(4-methyl-3-nitro-phenyl)-1,3-dihydro-benzo[e][1,4]diazepin-2-one

1-Methyl-5-(3-nitro-phenyl)-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin-2-one

5-(3-Amino-phenyl)-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4]diazepin -2-one

3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzonitrile

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzonitrile

3-(1-Methyl-2-oxo-8-phenoxy-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide

3-[7-(2-Chloro-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(2-Methoxy-phenyl)-1-methyl-2-oxo-8-phenoxy-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide

3-[7-(5-Chloro,2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]- benzamide

3-[7-(2-Chloro,6-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]- benzamide

5-(3-Hex-1-ynyl-phenyl)-8-methoxy-1-methyl-7-phenyl-1,3-dihydro-benzo[e][1,4] diazepin-2-one

{3-[3-(8-Methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-phenyl]-prop-2-ynyl}-carbamic acid tert-butyl ester,

and salts thereof.

17. Compounds selected in the group consisting of :
3-[7-(2,6-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[7-(2,5-dimethoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[8-methoxy-7-(4-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[8-methoxy-7-(2-methoxy-phenyl)-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide, 3-[7-(2-chloro-phenyl)-8-methoxy-1-methyl-2-oxo-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl]-benzamide and 3-(8-methoxy-1-methyl-2-oxo-7-phenyl-2,3-dihydro-1H-benzo[e][1,4]diazepin-5-yl)-benzamide.

18. A pharmaceutical composition comprising at least one compound as defined in one of the preceding claims, and a pharmaceutically acceptable vehicle or support.

19. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of diseases associated with abnormal regulation of intracellular cAMP and/or cGMP rate.

20. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of diseases of the central nervous system, especially connected with an abnormal regulation of neurotransmitter effect or a release deficiency of one of the neurotransmitters.

21. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of a disease selected in the group consisting of depression, schizophrenia, autism, anxiety, bipolar disorder, attention deficit hyperactivity disorder (ADHD), sleeping disorders, obsessive compulsive disorders (OCD), fibromyalgia, Tourette's syndrome, drug or alcohol dependence, epilepsia, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, obesity, and Lewy body dementia.

22. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of a disease of the peripheral nervous system or peripheral organs.

23. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of a disease selected in the group consisting of reduced natriuria pathologies, acute renal or liver failure, liver dysfunction, and pathologies due to or involving prolactin release dysfunction, such as restless leg syndrom, rheumatic, allergic or autoinflammatory disorders, such as rheumatoid arthritis, rhinitis, and asthma.

24. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of, central or peripheral, acute or chronic diseases.

25. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of memory deficiency or cognitive disorders.

26. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of neuro-degenerative diseases.

27. The use of a compound of any one of the claims 1-17 or a pharmaceutical salt thereof for the preparation of a pharmaceutical composition for the treatment of obesity.

PATENT APPLICATION

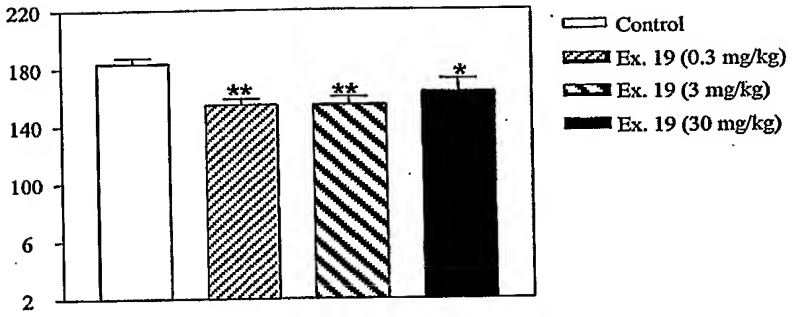
Phosphodiesterase Inhibitors, Preparation and Therapeutic Use Thereof

NEURO3D

ABSTRACT

The invention relates to compounds having PDE2 inhibitory activities, as well as therapeutic methods by administering said compounds, in particular for treating various diseases of the central or peripheral nervous system. It further deals with pharmaceutical compositions comprising said compounds and methods for preparing said compounds.

FIGURE 1


220
180
140
100
6
2
**
**
*
Control
Ex. 19 (0.3 mg/kg)
Ex. 19 (3 mg/kg)
Ex. 19 (30 mg/kg)